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TRANSACTIONS & STUDIES

of the

College of Physicians of Philadelphia

Volume 22

(Fourth Series)

Number 1

(June 1954)

Reflections on Pituitary Infantilism*

By SIR GEOFFREY JEFFERSON, F.R.S.

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THE isolation chemically of six of the hormones of the anterior lobe or glandular part of the hypophysis permits us all, the neuro-surgeons in particular, to review our pituitary material and to see which of the suspected actions of the gland have a firm foundation in truth and to question with better reason some of the others.

It seemed that the subject of infantilism might prove to be of interest to others as well as to the surgical craftsman. All the examples of retarded growth and arrested sexual development to be presented to-day had a uniform pathological causation, namely, tumours arising in those epithelial rests, which are so common a feature of the normal hypophysis and of the infundibular region. They were carefully studied by H. T. Carmichael (1931) and examples given by Susman (1932). The resultant tumours have been variously called Rathke pouch cysts, Erdheim tumour (an eponymous title recalling the first recognition of its true nature by the Viennese pathologist), tumours of the pituitary duct, adamantinoma or cranio-pharyngioma (Cushing). The accuracy of this last title, in such common use to-day, was called in question by Ingraham and Scott (1946), though they rightly made no plea for its abandonment since it is so firmly established.

These tumours behave in very variable manners. Some remain more or less confined to the sella, with relatively small supra-sellar extensions. That type gives us our best surgical results. It mimics the clinical picture presented by pituitary adenomas—making itself known by pressure on the optic chiasma and by more or less of inhibition of sexual maturation or, in maturity, of sexual activity. So localized a tumour development as this is uncommon, having occurred in no more than some six of my own cases. In the majority of the cases the tumour proliferates as an irregular mass which stretches the chiasma and rises behind it to fill more or less completely the third ventricle and interpeduncular space, and even to creep over the stunted dorsum sellae to descend into the posterior fossa on the front of the pons. Carmichael's studies showed very clearly that a tumour might take origin in the upper hypophyseal stalk or tuber and then would have every advantage in plastering itself in the most surgically inaccessible, and physiologically most dangerous place. It is these roving propensities which give the tumours the high mortality (from 30–40 per cent) that has been

* James M. Anders Lecture XXX, College of Physicians of Philadelphia, 2 December 1953.

the common experience of surgeons and makes it perhaps the most dreaded of intracranial tumours. It is a pity that it should be so, since although it occurs at any age it is most common in young people. Frazier and Alpers in reporting 14 cases in 1931 recorded 70% of their patients as under 20 years of age, and 12 of F. C. Grant's 30 patients were under 24 and 9 showed the Fröhlich syndrome. The following table shows the position today:

AGE INCIDENCE

Age	Cushing 92 cases	Love and Marshall 100 cases	Jefferson 75 cases
0–10	14	19	13
11–20	29	34	24
21–30	19	12	17
31–40	13	15	7
41–50	9	11	6
51–60	6	8	5
60 plus	2	1	3

Evidently this is a tumour, commonest in the second decade, which becomes progressively rarer as age advances, but which can be encountered in those late in life. A common feature of these tumours is their tendency not only to cause sellar abnormality but to calcify, presenting tufts of intra- and, more often, of supra-sellar calcification which are tell-tales in giving away the diagnosis radiologically.

I propose to concentrate my attention on the younger groups, since it is these which most clearly give a clinical demonstration of some of the functions, endocrinal and neurological, of the hypophysis and anterior hypothalamus. Except incidentally no special reference will be made to field defects presented by these tumours. They were the subject of a special study by Wagener and Grafton Love (1943) on 23 cranio-pharyngiomas and 6 epidermoids. Now, although these latter are, strictly speaking, epithelial rest tumours, they behave differently from the cranio-pharyngiomas in that they do not wander and, behaving like the most amenable kinds of pituitary adenoma, have a negligible operative mortality. Homonymous defects are certainly commoner in the cranio-pharyngiomas than in pituitary adenomas, and papilloedema with opening of the cranial sutures is more often encountered in the pituitary anlage tumours. As a consequence, headache and vomiting are the leading symptoms and often the only ones. It transpires that the visual defects caused by cranio-pharyngiomas are the result often of a combination of papilloedema and of direct chiasmal and even tract compression. I had hoped to be able to produce percentages of the significant field changes characteristic of these tumours but they are so variable that they do not easily allow of arrangements in groups. The analysis made by Wagener and Love tallies with my own experience.

THE PITUITARY HORMONES

The chemically identified hormones are given in the following table. The disparity in the notation is only apparent, since the gonadotrophins are known to be essentially the follicle stimulating and luteinizing hormones. Our chief interest today will be in growth stimulating, the gonadotrophic and adrenocortical hormones.

HORMONE	EVANS	SELYE	GADDUM AND LORAINE
Growth	+	+	+
Thyrotrophic	+	+	−
Gonadotrophic	+	−	+
F.S.H.	−	+	+
Luteinizing	+	+	+
Adrenocortical	+	+	+
Prolactin	+	+	+
Chromatophore	−	+	−

Since the majority of my own cases were dealt with before any reliable method of biological hormonal assay was practicable some of my evidence must be oblique. And even now we await with great interest the day when some relatively simple and quick method of laboratory estimation will be possible on blood samples.

The time factor is of great importance in a patient whose condition calls urgently for surgery. All the world knows that as far as concerns both immediate and long survival the

pituitary-adrenal linkage is the most important and here fortunately in the estimation of 17 keto-steroids, in the Kepler water tests and in the insulin-sensitivity test, we have reasonably swift methods of discovering how far off or how nearly adrenal failure and Simmonds' disease threaten our pituitary tumour subjects. I shall return to this subject later. For the moment I wish to direct attention to the growth factor and shall shortly show pictures of a series of patients whose physical status conforms to the pattern of infantilism. I propose also to turn to the other end of the scale and present three patients with the gigantism which Brissaud and Henri Meige (1895) showed so long ago to be due to overaction of the pituitary in youth.[1] Before presenting these cases it would be as well to review briefly the present state of our knowledge about the growth hormone which was isolated in pure chemical form by C. H. Li, Evans and Simpson in 1945. It is a protein relatively insoluble in water. In his Harvey lecture (1952) Li lists the following amongst the many functions to which the growth hormone contributes:

1. Promotion of continuous growth in normal and hypophysectomised rats.

2. Enhancement of chondrogenesis and osteogenesis in the epiphyseal cartilage of the tibia. Such an increase can be used as an indication of the presence of growth hormone in young animals.

3. Increase of protein and water in all the animals' tissues leading to increased body weight. At the same time body fat is reduced. These changes indicate true growth.

4. Increased uptake and turn-over of phosphorus and calcium in bone.

5. Production of glycosuria and hyperglycaemia in cats and dogs, with production of permanent diabetes in dogs if growth hormone is injected for a long period.

6. The giving of thyroxin enhances growth activity if given with growth hormone; the effect of the two combined is superior to either given alone.

With these facts in mind we shall expect to see our giants of relatively slender build, even if they are tall, and probably susceptible to glycosuria, though none of my own showed that. The reverse of the above changes will be the likely result of any lesion that inhibits the activity of the hypophysis—the subjects should be undersized, and remembering the decrease in fat caused by injection of growth hormone, its absence should cause hypopituitary obesity. This last remark would fall right into line with Fröhlich's syndrome, but my own experience has proved that real obesity is uncommon in those suffering from pituitary infantilism and few people who talk of Fröhlich's dystrophia adiposo-genitalis syndrome seem to understand what it really implies. Many think that given any very fat person the excess of adipose tissue is very likely due to pituitary dysfunction. There is no reliable evidence that this is so.

It would be as well to interpolate here some reference to the work of G. W. Harris (1951) on the activation of the pituitary. Harris has produced experimental evidence suggesting that the hypothalamus drives the anterior pituitary by means of a chemical stimulant proceeding down the portal vascular system known to exist in the pituitary stalk. Harris states that the belief that the blood flows

[1] Theirs is a fascinating story, beautifully told—how they were attracted by the painting of the Giant outside the carnival booth, but, say they, "mediocre though the painting was, there was a significant thing—it was all jaw." They go in and find the 47-year-old giant now much enfeebled and reluctant to be examined. They found out that he is indeed a pronounced acromegalic, this man 212 cms high at age 21, and later 220! (they say). They come out with some very positive statements. Certainly all acromegalics are not giants. Gigantism and acromegaly are one and the same disease, but what has not been sufficiently considered in the reports of acromegaly and of gigantism is the *age* at which they start. If the time at which the disease starts belongs to adolescence and youth, the result is gigantism, not acromegaly. If, finally, having appeared in the time of youth during which the body continues to increase, it impinges on the time when one has become man, in other words, on the period which no longer brings osteogenic development, the result is a combination of acromegaly and gigantism. They conclude the paper with a striking phrase: "Acromegaly is the gigantism of the adult; gigantism is the acromegaly of the adolescent."

upwards along this portal system is wrong. It is in the opposite direction. It is the hypothalamus which calls the secretion from the anterior pituitary gland. It is well-known that all the endocrine glands are transplantable and will function in new situations except the hypophysis. Harris showed that it will only secrete if it is replaced in contact with the stalk which becomes attached to it again. Only when put back where it belongs, is polyglandular atrophy—of thyroid, gonads, and adrenals—prevented. This may have a particular significance in pituitary infantilism because the cranio-pharyngiomas are remarkable for their supra-sellar extension, their interference with the pituitary stalk, their upward invaginations of the tuberal region and intrusion into the third ventricle. As a consequence we might assume that they might interfere with pituitary activation (e.g., the growth hormone) long before they are large enough to give signs in other ways.

PITUITARY GIGANTISM

There is in the Museum of this College the superb skeleton of the Kentucky or Mütter giant described by McFarland (1938). He was over 7 ft. tall and lived to the age of 22. Humberd (1937) has interested himself in giants and has written well about them. He quotes the records of the U. S. Army Recruitment Board of the first World War who rejected only 7 of over 3.75 million recruits between the ages of 18 and 30 as being above the Army limit for height, which was 6 ft. 6 ins. The unanswered question is—what constitutes gigantism, at what height is a person to be labelled a giant? There is no undebatable reply. What we do know for certain is that the giants of artistic creation as portrayed in children's stories and picture books, men of immense height and colossal strength, do not exist. But neither does anything resembling them on a smaller scale exist either. The great majority of those that have been reported in medical literature have come under observation because they were failing physically. Most, as in Brissaud and Henri Meige's case, have been weaker than men of lesser stature and a number of them are said to be no more than 21 years old at death. Some have been exceptionally strong whilst adolescent, as was the Alton giant (Humberd, 1937), and then lose their power. Evidently everything depends on the duration of the over-secretion of growth hormone; if there is an active adenoma it will kill them in the long-run. Krabbe and Matthiasson (1936) suggested that it would be more rational to speak of "pathological augmentation of growth" and to avoid the more sensational name of gigantism. I agree with this but shall, I fear, continue to speak of giants, realising that unusual height may be sometimes an inherited tendency without pathological significance.

Of my 3 cases, the first, a boy of 19, survived until he was 40 though he had been a very feeble creature unable to do anything but the lightest work all his life. He was 7 ft. high, his metabolic state was normal and his pituitary fossa normal in size when he was investigated at the age of 22.

The second is a girl, now aged 28, who was 6 ft. 4 ins. at the age of 14 and who grew only another 4 ins. in the next 14 years. She is a well and active girl apart from the arthritic changes so common in hyper-pituitarism whether showing itself as acromegaly or as gigantism. Professor Kellgren in Manchester has made a special study of the curious collagenous changes found in acromegalics. It appears to have chemical characteristics of its own and affecting the blood-vessels may be a contributory cause to the vascular hypertension which is a distinctive and sometimes a fatal feature in acromegalics.

The third giant is a boy, now aged 20, who is 6 ft. 11 ins. tall. He is in bad shape with a large sella, bitemporal hemianopia, very severe joint stages and a remarkable osteomalacia of the pelvis allowing the femoral heads to push the acetabula inwards. He has normal steroid chemistry and gonadotrophic output, but undeveloped genitals. He does some paper work at home but can only walk a few yards.

It is unlikely that he will survive for long. All three of these patients were on the slender side, with somewhat lean limbs. None of them was diabetic. All were sexually immature; the girl had never menstruated and had, like the others, scanty body hair.

PITUITARY INFANTILISM

The ages of the patients with cranio-pharyngiomas have been given; there were 54 who were under 30 and might be expected to show signs of pituitary underaction. This was the case in 48. The reason why there is not 100 per cent infantilism depends on this: that in several we must assume that although the gland or its tuberal connections were considerably compressed it was not rendered entirely inactive. This was proved to be the case in some who came to autopsy and in whom a fairly thick capsule of normal gland formed a nest in which the base of the cranio-pharyngioma lay (*Fig. 1*).

The average height of those aged 15 to 21 was 52 ins. (tallest 58 ins., shortest 46). The standard mean height of British school children at 13 years of age is 59 to 60 ins., an increase of 2.5 to 3.5 ins. since 1880 (E. B. Clements, 1953). At 8 the boys today measure 50.1 ins., the girls 49.4 ins., at 10, 53.6 ins. and 53.7 ins., respectively, and at 13 the girls are slightly the taller and 2 lbs. heavier than the boys.

These figures confirm the fact that the person with a cranio-pharyngioma is so much undersized that even if he is now aged 20 the interference with pituitary growth hormone production must have begun perhaps 10 years or more before. Just as the date of onset of amenorrhoea dates the development of a pituitary tumour better than the appearance of chiasmal compression, so with these anlage tumours the arrest or retardation of growth is the best evidence of the start of the tumour. Interference with the pituitary growth hormone produces not only an undersized individual but one usually with long, slender limbs and a comparatively short and often lean body (*Fig. 2*). Sexual development may occur,

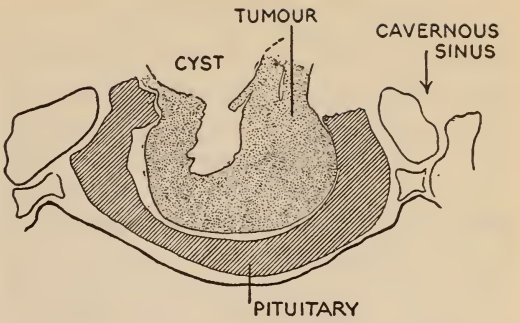

Fig. 1. Cranio-pharyngioma Nesting in Capsule of Apparently Active Pituitary—Female, Aged 25, Fully Grown, Sexually Normal.

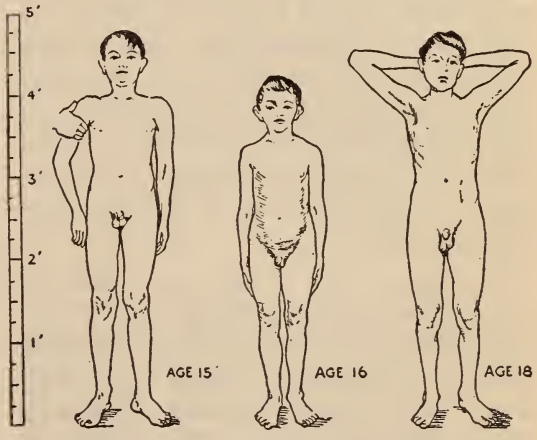

Fig. 2. Pituitary Infantilism. Average Height of Boys at 13 Yrs is 5 Feet.

for the reasons given, but usually it is lacking save for a few sparse hairs on the body. In the male the genitalia remain small and, in the female, if menstruation has started it usually stops when the tumour grows actively, just as happens with chromophobe adenomas. An interesting feature of my patients in the 13–21 age band has been that they reach a certain height, about 4 ft. odd, and then stop. It is as if they were able to attain so many inches of growth even though they must have been under-supplied with growth hormone whilst still growing. An observation of C. H. Li's may have a bearing on this fact. It is to the effect that cessation of growth does not occur in young rats until about 30 days after hypophysectomy, which is quite a time in a rat's life.

OBESITY AND THE PITUITARY

None of my infantile cases, save one, has been really fat; it was more common for them to be thin than fat. This is against the common belief that Fröhlich's syndrome means a really obese body. A glance at the photograph published, in 1901, of Fröhlich's patient shows[2] that although his abdomen was a shade on the plump side neither his torso nor his limbs could be regarded as being those of a strikingly obese subject. We see many, many patients in the ordinary run of Hospital practice who are vastly fatter than Fröhlich's patient ever was and yet it never occurs to anybody that their pituitary physiology is abnormal—nor is it. The story is the same with the chromophobe adenomas, of whom not more than 20 per cent claim to have gained over 14–20 lbs. in weight during 4 or 5 years, and everyone knows that that can happen to many of us for no very apparent reason.

One cannot have it both ways with the pituitary and obesity. According to one rubric, hypo-pituitarism leads to obesity; according to another, if one has practically no pituitary at all one becomes emaciated (Simmonds' disease). It was one of the most striking conclusions of H. Sheehan's work on post-partum necrosis of the pituitary and resultant Simmonds' disease that these women were nothing like as emaciated as had been believed to be the rule in this dangerous condition. Very many of them were plump though not obese and little altered in physique except for the tell-tale permanent amenorrhoea, vaginal atrophy and the eventual loss of all body hair. The absence of hair seems to have an adrenal linkage as well as a gonadal and is certainly a danger signal. Quite clearly anyone relying on emaciation as the sign most suspicious of Simmonds' disease is fated to miss the diagnosis most of the time. I can only conclude from my experience of 400 pituitary tumours of all kinds that only 2 exceedingly fat persons had pituitary tumours. I am sure that the records of the surgery of gall-stones and umbilical hernias could produce figures that surpassed mine in that way. In the series of 15 undersized individuals whose photographs have just been shown one was fat, two were plump and 12 were slender. Real obesity is therefore not often met with in hypo-pituitary subjects and never in hyper-pituitary. I conclude that the pituitary has little to do with fat deposition.

[2] See, for example, the reprint of it in A.R.N.M.D. 20: xxii, 1940.

INFANTILISM AND ITS EFFECTS ON THE SOCIAL HISTORY AND PSYCHOLOGICAL OUTLOOK

Most of these infantile subjects, untroubled as they are by sexual development and the emotional urges dependent on it, seem on the surface to be serene and happy people. And so they are up to a point; but life leaves them behind, their friends grow up, marry, and leave their undeveloped school friend, who must turn inwards to his mother and the family circle for support and amusement. I can best illustrate this and much that I have said above by the following case history:

Chas. A. H., aged 29, male, (191/41), industrial chemist, admitted to the University Department of Neuro-surgery, Manchester Royal Infirmary, 25/7/41, complaining of attacks of headache and vomiting intermittently for a period of 20 years. These were severe, lasting several days. Up to 9 years of age he was perfectly well. Was 9½ lb. baby. Above average height at school, fond of games; in the past 13 years had grown 6 ins. and thought he was still growing at 29. Was now 5 ft. 2 ins. Many weeks between attacks, continued all his life but for 5 years might be less frequent and severe. At age of 12 began with polydipsia, which continued for 12 years, when pitressin stopped it. Mother said he had never been the same since an undiagnosed illness at age of 10, when for 9 months he vomited, had bad headaches, took no solid food for 6 months and was away from school. He started bed-wetting and continued it for 10 years and left boarding-school on that account at 15½ years. He had always felt tired, lacking in energy, but did well at Technical School. In short, his life had been one not quite of invalidism but

of a remitting illness that made his health uncertain. As he grew older his retarded growth, not only in height but in robustness and his pituitary pallor gave him a delicate look. His recurrent sicknesses interfered with his taking part in games after he was 10 and he became more and more isolated from friends. This was more pronounced still after his twenties had been reached; he remained very much with his mother, who protected him and was his companion more than boys and girls of his own age. He was not interested in girls. His sexual development physically was lacking, the genitalia infantile with no body hair. His friends got married and he continued to be withdrawn socially, not because he chose to be but because his boyish and frail appearance, his unbroken voice and intermittent illness made him "different." He was, as most of these pituitary infantiles are, a singularly pleasant young man to talk with, shy, modest and unassuming. He was, not unnaturally, hurt when people spoke to him as if he were the office boy at the works where he had an important post as a chemist. His lack of social life made him read a great deal, his choice being mathematics, astronomy, detective stories of the better sort and good novels, rather than the adventure and youthful stories that his appearance suggested would be his choice. He was distinctly touchy on this point. In fact this patient was a remarkably good example of the psychological and social difficulties that beset the physically abnormal. With an intelligence above the average, with an outlook on life undisturbed by the emotional swings of sexual maturity, with a gentle and pleasant mother, he was nevertheless far from happy. The world had its own ways and usages and although he wished to be within the circle his appearance and lack of robustness made him unsatisfied, because he was an involuntary "Peter Pan." The "boy who never grew up" was not content, because his failure to mature was not of his own choosing.

What is true of this case could be written almost word for word for most if not all of these cases. There are individual variants, of course; there must be, because each one of us inherits a basic personality which is different and an aptness to learn which is variable. Not all are as easily hurt or as sad as was Charles H., but they all suffer from the same social impediments and are well aware of the fact without realizing its causes.

To return to the physical findings—his stunted growth has been referred to; to this must be added his long, slender limbs, his long fingers, his relatively short trunk, the fine, smooth and almost hairless skin, the absence of fat accumulation to soften his contour, and the peculiar, slightly yellowish pallor that looks like pernicious anaemia. His blood picture was normal, as is usual in the pale pituitary subject. The optic discs presented only slight pallor, the visual fields showed a shallow bitemporal cut-off in the smaller isopters; visual acuity was 6/6 in both eyes. X-rays of the sella showed it to be grossly enlarged and rising 1 in. above it was a faint curved calcified line, evidently in the dome of cranio-pharyngeal cyst.

Through a transfrontal flap, on 16/9/41, a yellowish looking cyst was found protruding between the long, stretched optic nerves, for the chiasma was "post-fixed." The cyst wall was tough and was excised, its contents were a yellow, thick, mud-like, amorphous substance with no characters histologically.

This young man made an uninterrupted recovery. He was put on testosterone tablets and was re-examined 9 years later. He was now 38. He had grown 3 ins. since he was 29 and presumably because of the hormone therapy his genital development had advanced materially. Pubic hair had appeared, though it was not abundant and was female in distribution. He was much more confident and robust in his manner. He had had no important attacks of sickness or headache.

OPERATIVE RESULTS

It was not my intention to go into the surgery of the cranio-pharyngiomas, which is a dark page in most surgeons' records. The mortality in my series of 75 cases was 39 per cent, which is much the same as that reported by

Love and Marshall (1950) from the Mayo Clinic. They found 108 cases in their records, between the years 1916–1940, 96 of whom were operated upon with a mortality of 40 per cent. F. C. Grant (1948) had a slightly lower death rate, 35 per cent in 30 cases. Ingraham and Scott (1946) in an admirable account of 16 cases reported only 1 death, but 11 of the 16 died subsequently and they had only 2 long-date survivors. If the surgeon could only see before he operates how widely some of these tumours have spread themselves over the sella and middle and even posterior fossa, not to mention their adhesion to the hypothalamus, he would avoid mortality by refusing to do anything. But this is a hard decision to make in the case of a young person, and few of us can resist the appeal of a young life in danger. I have no doubt that some are best treated by ventriculo-cisternostomy (Torkildsen's operation), leaving this ubiquitous tumour untouched.

CONCLUSIONS

It can be concluded that in spite of the compression of the anterior lobe of the pituitary by congenital tumours there is rarely any urgent threat to life directly from lack of pituitary hormone. Were it otherwise we should find these patients primarily in the medical wards of our Hospitals as cases of Simmonds' or supposed Addison's disease. But although apituitarism may threaten in the background, the symptoms that bring them to Hospital are those of raised intra-cranial pressure or visual deficiencies. Experiences with pituitary necrosis precipitated by post-partum haemorrhage or other puerperal disaster have taught us that length of survival is related to the quantity of pituitary remaining. We must admit that we do not know how long a patient could live with no pituitary at all. When hypophysectomies are done for malignant disease everything is done to supply adequate adrenal cortical hormone, so we learn little there. We can say that the subjects would probably live unaided a few weeks or many months or possibly years, just as hypophysectomised animals have done. In the cases with pituitary infantilism it is likely that a certain amount of pituitary hormones has been secreted. But if they are all as depressed as the growth hormone it looks as if human beings can get by for years with a minimum of the others. We do not know yet by biological or chemical assays how much of any hormone these pituitary infantiles are producing. We shall find that out in the years immediately ahead. It is quite certain that the cranio-pharyngiomas kill chiefly by spreading into the post-chiasmal region and up into the third ventricle. Attempts to dissect them out of such places often lead to rapid death with hyperthermia. Others who survive may live a few days and then fade out rapidly with what looks like an acute polyglandular deficit or some other disaster to the control of the body's chemistry, the nature of which has proved so far not identifiable. There is a challenge there that we must meet.

I have presented here the most unmistakeable gross clinical evidence that we have of abnormality of the pituitary hormones, namely, pathological growth and the more common infantilism. They are the best subjects from which to develop a pituitary discussion.

I have drawn attention for the first time to the effects of infantilism on the patient's social life and happiness.

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Physiological Behavior and Therapeutic Use of Plasma Volume Expanders*

By DICKINSON W. RICHARDS. M.D.

INTRODUCTION

THE honor of giving the Mary Scott Newbold Lecture to the College of Physicians of Philadelphia is one which I deeply appreciate. My subject, the Physiology and Therapeutic Uses of Plasma Volume Expanders, is, I am afraid, to a very large extent bringing coals to Newcastle, this field of research having been really centered in Philadelphia for many years. The work of Dr. Ravdin and his associates in particular has been one of the mainsprings of activity, with Dr. John Lockwood here during the War, and Dr. Rhoads, Dr. Vars, and their colleagues working almost continuously for more than a decade. Many others in the Philadelphia area have made important contributions.

I think that I should also say, by way of introduction, that this subject is being presented this evening with the realization that new lines of research in the treatment of injury and shock are now in progress, such as induced hypotension and hypothermia, which may be far-reaching and may alter or even invalidate some of the more conservative work of the recent past. It is hard to believe, however, that there will not be a place and a time for blood and fluid replacement in treatment of these conditions, or that the basic principles of such treatment will be greatly changed.

It is customary to begin any discussion of plasma expanders—formerly known as blood- or plasma-substitutes—by the statement that there is no substitute for blood. This is still the most important thing to say about plasma expanders, and all experience of recent years, both military and civilian, adds emphasis to it. For blood loss, the only logical and complete replacement is whole blood. Without oxygen-carrying power, any solution, however well it stays in the circulation, can only dilute the blood's most immediately essential component. The restoration of blood volume is, of course, a vital necessity in shock, to maintain blood flow and interchange of body fluids; but without restoration of hemoglobin it is only a temporary expedient.

But it must be emphasized equally that the blood administered must be of very particular and special quality. It must be compatible, fresh, sterile, and in good physicochemical condition. It must be also sufficient in amount. It was the limitation in one or more of these aspects of quality and availability of whole blood that originally brought the plasma expanders into being as clinical therapeutic agents, and that has resulted since in their varying stages of importance or unimportance, depending upon the urgency of the need for blood replacement, as the general scene has shifted between war and peace. All this is a matter of history. The development of "blood substitutes" has progressed from the early and tentative studies with gum acacia in World War I, through the vast achievement in the development of plasma in World War II, and more recently to the studies of artificial expanders, revived when the Korean conflict began.

During the past three years there has been considerable progress in knowledge of the nature and performance of these various artificial plasma expanders. Our ideas have changed rather profoundly, in some respects,

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and in the course of these investigations a good deal of physiological information about body fluids, and about the disposal of foreign substances, has been gained. This is what I shall review briefly this evening, and with this knowledge attempt to reorient the position of the artificial plasma expanders in the whole scheme of blood replacement therapy.

To state the matter in more specific terms, there are three large problems to be solved: (1) the preservation of whole blood for long periods —by far the most important problem, and the most difficult; (2) the effective sterilization of human plasma; (3) the development of a wholly satisfactory artificial plasma expander. It is this last with which we are now concerned.

By way of background, a little of the historical development in this field may be of interest, and may also add appreciably to our understanding. The beginnings take us back almost a century. In 1863, Carl Ludwig (1) found that he could perfuse the kidney of a pig with gum acacia solutions, and obtain urine formation, without producing edema of the kidney tissues. In the same laboratory a few years later Bowditch (2) noted that frog hearts beat normally when perfused with fresh serum, developed arrhythmias as the serum aged, to return to normal beat again with perfusion of fresh serum. He obtained a normally beating heart also with gum acacia in saline. Through the next half century, various protein, colloid, and electrolyte solutions were experimented with in animals, empirically at first, then with increasing knowledge.

Clinically, Hogan (3) administered gelatin-saline solutions successfully in 1915, and Hurwitz (4) followed with acacia two years later. Through the interest of Bayliss, this latter product came into fairly extensive use toward the end of World War I, and in subsequent years its properties were more fully studied (5). It is of interest, in retrospect, how analogous the findings with acacia were, to those of subsequent investigations with dextran and PVP. Being a polysaccharide, acacia gave anaphylactic reactions under certain conditions. It was found not to be metabolized, and was stored largely in the liver. This, and a few toxic clinical reactions, eventually brought acacia into disrepute, and its clinical use after the middle 'thirties gradually declined. These studies with acacia (5), however, carried on over so many years, have constituted an important contribution, which I believe we have somewhat underestimated in recent years. I shall have occasion later to refer to some of these findings.

The outbreak of World War II found another product well established for the treatment of injury with shock, namely human plasma. The outstanding achievement in the stabilization and preservation of human plasma, and in making it available for military and civilian use—an achievement due in major part to the remarkable genius and indefatigable energy of the late Dr. Edwin Cohn—does not need to be detailed here. It can, however, be said that neither the whole blood development—important though it is—nor the current difficulties with the contaminating hepatitis virus, should in any way detract from the wide and still increasing significance of the plasma and plasma fractionation program.

One of the early features, in particular, of this work deserves a survey and review, in any overall evaluation of plasma volume expanders.

It is rare, in the development of a therapeutic agent, that the ideal product is found first, and that subsequently the major effort is devoted to studying makeshifts. This, however, seems to have been the case with the plasma expanders.

As Edwin Cohn and his colleagues got under way with their experiments in plasma fractionation, one of the first and most easily separated fractions was the albumin (6). As this contained most of the osmotic activity, it was predicted that it would be a good plasma substitute or expander, and such in fact it was. *Figure 1* is taken from one of many series of studies of patients with injury and shock during the war, to whom albumin solution was given (7). It will be seen that plasma volume increased satisfactorily, and was maintained,

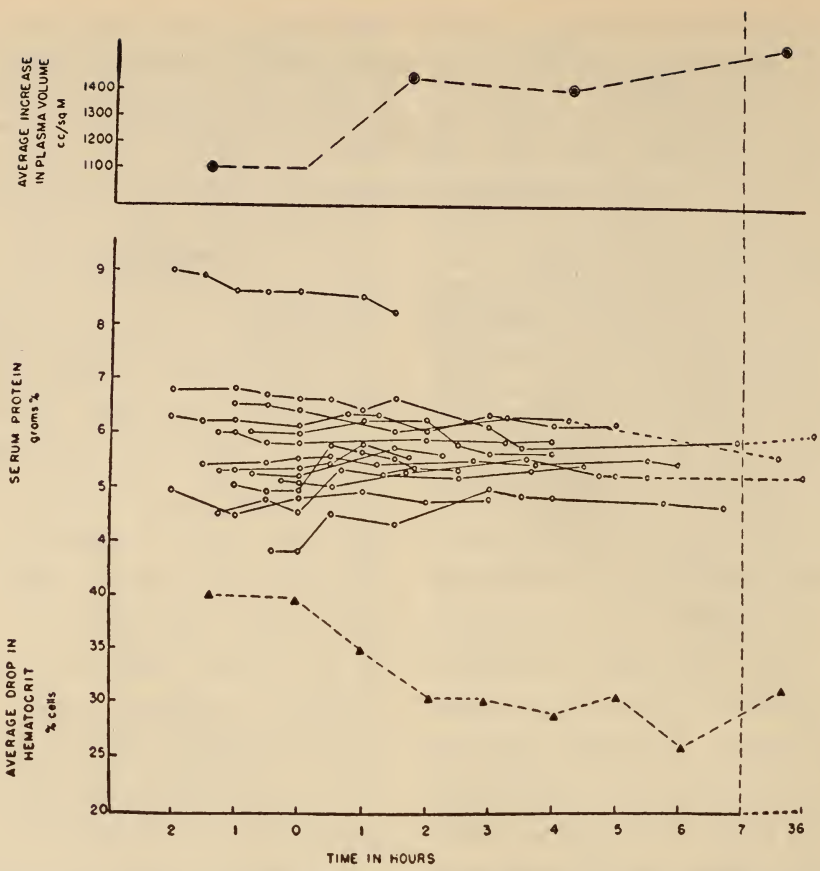

FIG. 1. INCREASE IN PLASMA VOLUME PRODUCED BY INTRAVENOUS ADMINISTRATION OF 50 GRAMS OF HUMAN ALBUMIN IN 5 PER CENT SOLUTION, TO A GROUP OF PATIENTS WITH INJURY AND SHOCK.

Upper curve: average plasma volume (expressed as cc. per square meter of body surface) before and at intervals after infusion. Middle curves: serum protein concentrations of each case. Lower curve: average hematocrit levels, before and at intervals after infusion. (From Cournand, Noble, *et al.* (7)).

while plasma protein concentrations remained level. Hematocrit, of course, decreased.

The product, made up in 25 per cent solution, was and is convenient and easily handled, usually used diluted to isotonic or 5 per cent concentration. Most important, it has been recently shown that the cold ethanol process, which is the standard method of separation, followed by heating, effectively destroys the hepatitis virus. At the present time, the large military stocks of human lyophilized plasma are being reworked, with the albumin and gamma globulin separated, each for its own specific uses.

Let us review the simple but very specific properties of this human albumin solution. It is a human protein, and is rarely antigenic. It is homogeneous and constant in composition. Its molecular weight of 68,000 is well above the size of the glomerular filter. Albumin solutions flow freely, down to their actual freezing point. The solutions are stable over long periods. Being a natural human material, its metabolism in the body is no problem. Like other plasma constituents, albumin tends to move rapidly into and out of the extra-vascular tissue spaces. While this may theoretically limit the value of albumin as an immediate resuscitator of the circulation in shock, it will be of special benefit after this initial phase, since protein deficit is apt to be a large problem long after acute shock has been relieved. In the

TABLE 1

REQUIREMENTS FOR A SATISFACTORY PLASMA SUBSTITUTE

Blood Substitutes Committee of the National Research Council, 1942

Clinical Performance	1. Maintains a satisfactory oncotic pressure
Physical Properties	2. Viscosity suitable for intravenous injection
	3. Stable to temperature change
	4. Readily sterilized
	5. Unchanged after long storage
Safety. Toxicity	6. Free from pyrogens
	7. No immediate adverse effects
	8. Ultimately excreted, used, or deposited in the body so as not to cause organic derangement, immediate or delayed
	9. No antigenic properties
Manufacture	10. Can be produced with constant composition
	11. Reasonable in cost of production, and price

past, albumin was at a disadvantage because of increased cost of production. At present, in part because it does not require sterilization, I understand that, gram for gram of effective protein, there is but little difference in basic cost between dried plasma and concentrated albumin solution.

In view of all this, one might anticipate that human albumin solution will come into wider and more general use, as it certainly deserves to. It is also not unlikely that whole human plasma can be sterilized and so made available again. While this will make the artificial expanders less urgently needed, they are still an essential feature of any overall program: (1) human plasma and whole blood will never be adequate in amount in any large scale military action; (2) artificial expanders can be made more cheaply; (3) there may be certain respects in which the artificial expanders have temporary physiological advantage over human plasma.

Even early in World War II, it was apparent that the supply of plasma might be insufficient, and much attention was given to the development of a substitute. *Table 1* gives the general requirements for such a product, as prepared by the Blood Substitutes Committee of the National Research Council at that time. These are familiar to many of you. They were, and are today, very practical requirements, though in some, such as numbers 1 and 8, many details would have to be filled in. More about this presently.

Of many materials then tried, by far the most successful was a purified preparation of osseous gelatin. This substance, first studied in animals by Ringer in 1885 (5), and in man by Hogan during World War I (3), (as already noted), had been discarded in the years since, because of toxic reactions, probably due to the crude preparations used at the time. The World War II products, however, gave a good account of themselves, especially the more lightly hydrolyzed, or degraded, forms which behaved, in the main, not unlike plasma or albumin solutions. There were essentially no toxic effects, even with fairly large doses—several liters of 6% solution—and plasma volume was well sustained in wound shock and burns (8). A genuine difficulty was the products' viscosity, requiring warming almost to body temperature before it would run through a needle. More completely hydrolyzed gelatins, such as the P-90, of lower molecular size, had a plasma volume sustaining effect, but much less, sometimes only slightly more than saline solutions.

This was about the situation when the Korean conflict broke out. The emergency with respect to blood, plasma, and expanders was serious. Plasma stocks were insufficient for any large-scale demand, the blood program took time to build up, and no accepted plasma substitute was available except gelatin. This, being solid at cool temperatures, was unsuited to use in the field. As it turned out, the Red Cross rose to the occasion magnificently, as did the Army transport system, and blood and plasma were supplied to the military theatre in great quantity.

Then came the second crisis, caused by the

rapid increase in incidence of infectious hepatitis, apparently transmitted by at least a part of the pooled plasma lots used. The eventual incidence of the disease in 20 per cent of all persons receiving pooled plasma (9) may well have included cases developing the disease from other sources, but the infectivity of this plasma was unquestioned.

All this intensified the necessity of moving ahead with the plasma expander program. In the summer of 1950, an organization was set up by the Division of Medical Sciences of the National Research Council, and the greater part of the research in this field during the last three years has been either sponsored by or coordinated with this program. Many aspects of the problem have been studied.

In this same summer and autumn, as the Korean situation developed and the need for a good plasma expander appeared more urgent, one question arose immediately and that was, how good should this agent be, how well should it sustain plasma volume and for how long? This required an answer at once, regardless of theory. A criterion was set up, based partly on the approximate performance of human plasma, and partly on existing logistic need. It was estimated that 12 hours was about the duration required for such an expander in treatment of the wounded man. It was therefore decided that an adequate plasma expander should maintain the circulating blood volume by an amount equal to half the volume infused, for a period of 12 hours after infusion into normal subjects. The latter were taken, also arbitrarily, since normals were the only comparable human subjects generally available.

This requirement has been subsequently criticized, with some justification. We will come back to this later.

In 1950, besides gelatin, which was for the time being disqualified because of its viscosity, there were two plasma expanders, which had been invented and developed in Europe, dextran and polyvinyl pyrrolidone, or PVP; and the greater part of what has been learned about plasma expanders during this period has been derived from studies with these two agents.

The results with PVP have been in some respects simpler than those with dextran, and I will review PVP first, though the actual investigations have gone on concurrently.

POLYVINYL PYRROLIDONE

Polyvinyl pyrrolidone is a wholly synthetic chemical, whose basic structure, N-vinyl pyrrolidone, is a small 5-atom ring, produced by the reaction between acetylene, ammonia, and formaldehyde under pressure. It can be polymerized into molecules of almost any size desired. It was produced originally by Hecht and Weese in Germany (10) in 1943 as a plasma substitute, is still used to a considerable extent in Germany, and widely in France.

It gives a clear non-viscous solution, and is easily administered, a 3.5 per cent concentration in a balanced electrolyte solution being approximately iso-oncotic with plasma. In the human body it is practically inert, giving essentially no reactions of any kind. Studies by Van Slyke (11) in animals, by Hellman (12) in human subjects, and by Fine and Seligman (13) in both animals and human subjects, with a product containing a radioactive atom, either carbon (C^{14}) or iodine (I^{131}), have shown that it does not break down to form respired CO_2, and other evidence indicates also that PVP is not metabolized. PVP molecules carry but little electrical charge, and their performance in the body, including their excretion, is thus wholly conditioned by molecular size. This has been extensively studied, by Cannan, Fine, Vars, Hellman, Cournand, Warner (14), and others, both with commercial PVP's, and with specially prepared fractions of narrowly defined molecular sizes.

As ordinarily manufactured for clinical use, PVP has a rather wide range of molecular size, spreading from 10,000 through a median around 60,000 to an upper range of 100,000 and up. It is a long slender molecule, thus differing markedly from human albumin.

Warner (14) has analyzed the data of sev-

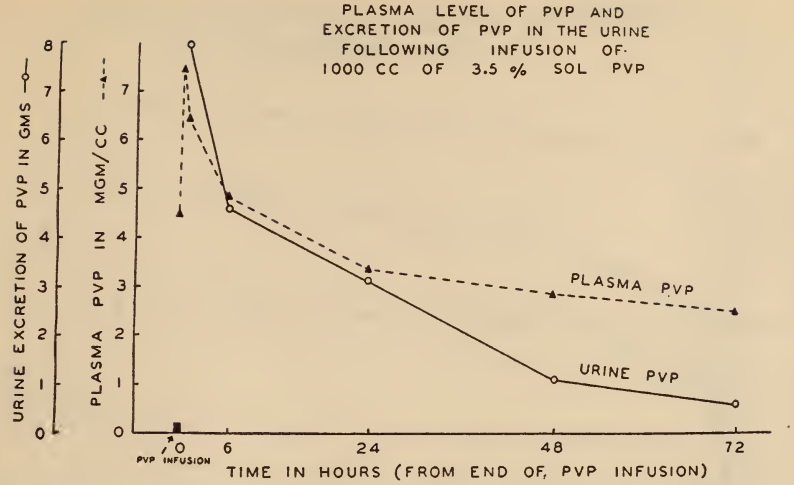
PLASMA LEVEL OF PVP AND
EXCRETION OF PVP IN THE URINE
FOLLOWING INFUSION OF
1000 CC OF 3.5 % SOL PVP
URINE EXCRETION OF PVP IN GMS
PLASMA PVP IN MGM/CC
PLASMA PVP
URINE PVP
PVP INFUSION
TIME IN HOURS (FROM END OF PVP INFUSION)

FIG. 2. PLASMA LEVELS AND URINARY EXCRETION OF POLYVINYL-PYRROLIDONE (PVP) SOLUTIONS.
Average values in six subjects. (From Bader, Kim, and Cournand (15)).

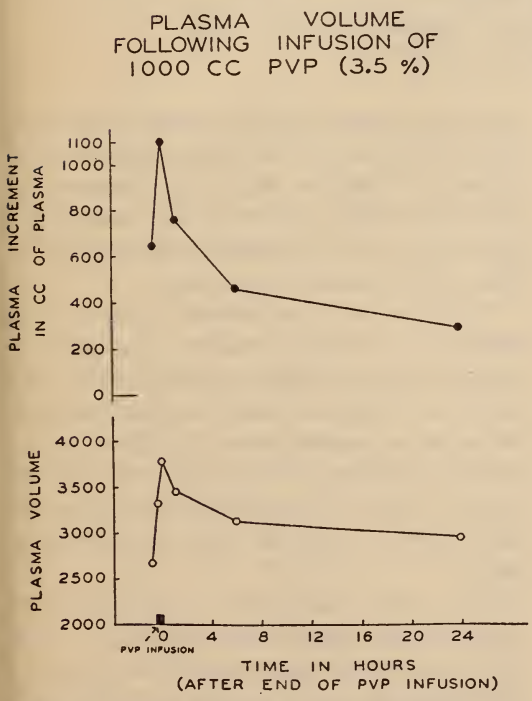
PLASMA VOLUME FOLLOWING INFUSION OF 1000 CC PVP (3.5 %)
PLASMA INCREMENT IN CC OF PLASMA
PLASMA VOLUME
PVP INFUSION
TIME IN HOURS
(AFTER END OF PVP INFUSION)

FIG. 3. PLASMA VOLUME VALUES FOLLOWING PVP INFUSIONS.

Average values in six subjects. (From Bader, Kim, and Cournand (15)).

eral investigators. The behavior of a therapeutic infusion of PVP can be described as follows:

Upon arrival in the blood-stream, the fraction of molecular size below about 25,000 begins very rapidly to be excreted by the kidneys but also diffuses rapidly into extracellular spaces. As a plasma expander this fraction is therefore of small value. About 35 per cent of a total injection of clinical PVP is excreted in 6 hours and this material has the low average molecular weight of 20,000. In subsequent hours the remainder of this low molecular weight fraction trickles gradually back from the tissue spaces into the blood and is excreted.

Larger molecules move much more slowly through the kidney filter, up to molecular weights of 35,000 to 40,000. Above 40,000 there is no renal excretion at all. The glomerular barrier is absolute. It is these larger molecular fractions which provide most of the plasma volume expansion or maintenance.

This retained material leaves the blood-stream slowly, a little less than half of it the first day, the rest still more slowly. Cournand (15) found measurable amounts in the blood after 21 days, though there was no significant effect on plasma volume after 48 hours.

Figure 2, from Cournand, Bader, and Kim (15), shows how the plasma levels of PVP decline gradually in the 72 hours following a 1000 cc. infusion of clinical PVP, and how the urinary excretion drops off to very low values after the first 24 hours. *Figure 3*, from the same study, shows that this agent is an effective

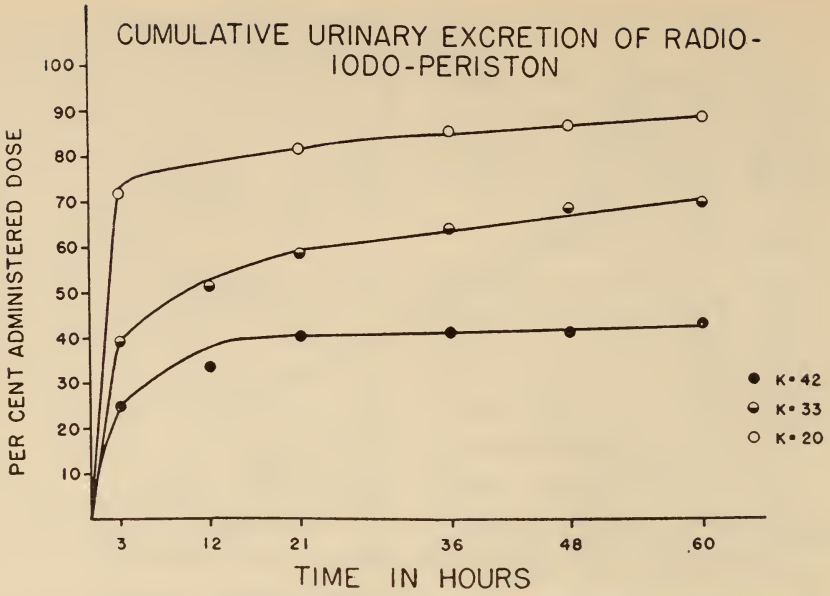

Fig. 4. Excretion of PVP of Varying Molecular Sizes. See text. (From Fine and Seligman (13)).

plasma volume expander, though falling a little short of the 50 per cent-in-12 hour requirement.

What happens to the non-excreted fraction of infused PVP? Studies with radioactively tagged material have confirmed other data that from 25 per cent to 40 per cent of infusions of clinical PVP is stored in the body, more or less indefinitely.

Separate studies with PVP solutions of different molecular sizes confirm these general findings. *Figure 4* is from an investigation by Fine and Seligman (13), on the excretion of Periston, or PVP, in dogs. A K-20 material has an average molecular weight about 20,000. This is over 90 per cent excreted, while the K-42 material, having a molecular weight ranging around 60,000 to 120,000 is only 40 per cent excreted. Similar findings have been obtained by Hellman in human subjects. *Figure 5*, also from Fine and Seligman (13), shows the difference in blood disappearance curves, between large and small molecular weight material. The stored PVP is widely distributed through most tissues (though not in the brain), largest amounts being in liver and skin. Fine (16) followed one patient for many months after a C^{14} tagged infusion. The excretion decreased progressively for a number of days, after which there was a tiny urinary excretion of some 3.5 mg. per day, that continued for about 15 months, then even that ceased. The greater part of the stored material was still in the patient's tissues at this time.

What are the consequences, if any, of this indefinite, perhaps permanent storage of a number of grams of inert material? This is one of the most important and serious questions before us in the evaluation of artificial plasma volume expanders. It may also be thought of as a part of a more general problem of the fate and effects of injected, inert, non-excretable solids.

The very considerable experience with acacia, already mentioned, is relevant to this question, as is the long period of time that has now passed since acacia was first administered; and a few of these acacia studies are perhaps worth reviewing. Like PVP, acacia is not metabolized, and after injection is largely stored, in greatest amount in the liver. The livers of injected animals or human subjects were not infrequently enlarged, sometimes tender. On examination the liver was yellow with large "foam" cells seen microscopically,

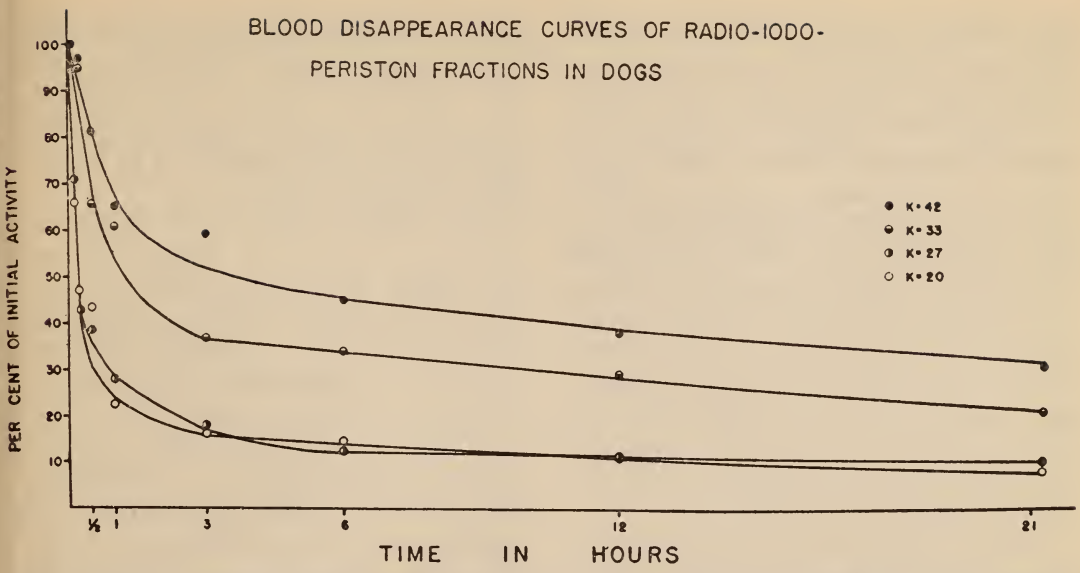

Fig. 5. Blood Disappearance Curves of PVP Fractions of Small (K-20), Medium (K-27,½ K-33) and Large (K-42) Molecular Size.

(From Fine and Seligman (13)).

in the reticuloendothelial system and elsewhere. In spite of these findings, the pathological consequences were remarkably benign. Smalley *et al.* (17) gave dogs 20 times therapeutic doses, and the animals were still in good health at the end of two years. Bollman (18) gave weekly injections to two dogs for 6 months, after which the dogs lived for ten years, still having enlarged "acacia livers." Heroic doses have also been given to human cases, chiefly to treat edema in nephrosis. Smalley and Binger (19) reported in 1944 on 109 patients treated from 1937–1943. One patient had received 570 grams, and 12 had received more than 200 grams. The average serum concentration of acacia after one year was still 100 mg./100 cc. Their conclusion was that acacia in these doses had had no harmful effect. One certainly cannot argue from this that the "acacia liver" is a good thing, but it is interesting to see how the body can handle some foreign materials, stored for long periods of time.

Returning to the problem of PVP storage, one can say that this also is not wholly answered, though strenuous efforts have been made. Epstein, Baker, Hanley, and Schlumberger (20), a team of pathologists and clinicians sponsored by the National Research Council, made a special search through Germany in 1951, looking for cases that had been treated with PVP, either recently or in the past, to find any chronic disease, of the liver or other organ, possibly related to PVP storage. Nothing even suspicious was turned up. As a part of this same study, Stenger (21) reexamined 48 children who had received injections of periston, or PVP, three to seven years previously. No abnormalities were noted in physical examination, blood, urine, flocculation tests or serum proteins. Continued and routine use of the material in France also confirms this apparent lack of toxicity. The experience in this country to date is the same, save for one recent histological finding by Altemeier (22). This is the occurrence in the livers of PVP-treated patients, of collections of blue-staining granular material, this material appearing only from 2 to 6 months after the PVP administration. There has been no good evidence of true liver damage, however, either histological or clinical.

There are reports, however, in the German literature of histologic changes occurring either

early or late following PVP administration (23). Most, though not all, of these cases had received relatively large doses. The majority of findings were in infants. The changes were chiefly the appearance in liver, lymph glands, kidney, or other tissues of vacuolated, frothy giant cells, similarly enlarged mononuclear cells, and reticular cells. This is quite similar to the type of change described after acacia, and is doubtless the manner in which the body handles sudden heavy doses of inert material. Whether these changes are ultimately damaging clinically or not, is not fully known, but thus far it appears, as was the case also with the "acacia livers," that essential tissue functions are remarkably little affected.

No final conclusion can be reached on PVP storage, but all evidence to date indicates that in limited dosage, the stored material is handled by the body without harmful effect.

DEXTRAN

Dextran as a plasma expander has presented a quite different series of problems, with much additional information resulting from its study.

Dextran is a polymerized sugar. It was first encountered as a contaminant in the beet sugar industry, being produced by certain species of bacteria. The dextrans have been the subject of considerable study. The Northern Regional Research Laboratory in Peoria (24), for example, has had for some years a large investigational program. It was from this Laboratory that the bacterial agent now used for the polymerizing process, leuconostoc mesenteroides B-512, was obtained.

Dextran was first suggested as a possible plasma expander by Groenwall and Ingelman in Sweden in 1941 (25), and subsequently developed by a number of investigators in that country. The production of the material is simple in principle: sucrose is polymerized by bacterial action into a viscous mass of high molecular weight, then hydrolyzed by acid down to molecular size suitable for clinical use.

Several years of clinical investigation in Sweden brought dextran into general acceptance in that country. There was a small incidence of immediate unfavorable side reactions, of the antigen-antibody type, including urticaria, sometimes backache, joint pains, fever, asthma, occasionally vasomotor collapse. These reactions were thought to be less frequent than with plasma.

When Swedish dextran was investigated in this country, however, by Scudder (26), and later Pulaski (27), in 1949–1950, these reactions were encountered much more frequently and were more severe, occurring in from 40 to 50 per cent of unanesthetized normal subjects. Dextran of American manufacture, on the other hand, was practically free from toxic reaction. Swedish dextran was of considerably higher molecular weight than American. This problem was then studied intensively by several groups; including those of Warren (28), Kabat (29), and Maurer (30). It was known that dextran as a polysaccharide developed cross-reactions with some of the pneumococcal polysaccharides. Kabat found that human subjects showing reactions to dextran also usually had skin sensitivities; that injection of as little as 1 mg. of certain dextrans would produce after three weeks both positive skin reactions and precipitins in the blood; and that all reactive tendencies appeared to be definitely increased with dextran of high molecular weight. Thus, native or unhydrolyzed dextran gave a high incidence of reactions, while American dextran of low molecular size caused few reactions. It was further shown in a special study using human volunteers, that one injection of dextran did not sensitize to subsequent injections. These findings were therefore quite reassuring so far as concerned clinical dextrans with relatively low molecular weights.

In brief, then, there would appear to be a rather limited average molecular size for dextran, which is large enough to sustain blood volume, without causing more than a rare incidence of antigenic reaction. As now approved by the Food and Drug Administration, the specifications for commercial dextran, in size distribution, are that its average molecular weight be 75,000 $\pm$ 25,000, the upper 5–10 per cent not to exceed 200,000, the lower 5–10 per

cent not less than 25,000. As with PVP, this is still a fairly broad range. In 6 per cent solution it is iso-oncotic, or, more accurately, slightly hyperoncotic.

In its performance in the human body, the chief difference between dextran and PVP is, of course, that dextran is metabolized and PVP is not.

Figure 6, from a paper by Rousselot and Metcalf (31), shows a typical dextran blood level and excretion curve. The dotted line, indicating the unaccounted for dextran, includes the amount still in the tissues plus the amount which has been metabolized and eliminated as CO_2 or other breakdown product. This is consistent with more exact data obtained with radioactive dextran. A number of such studies have been carried out, showing that about 70–75 per cent of injected clinical dextran is excreted, the remainder broken down, the C^{14} appearing progressively in expired CO_2 (32), in tissue amino acids, carbohydrates and fat (33); all but about 7 per cent metabolized in ten days, the rest in four or five weeks. There is therefore no storage of dextran.

The movement of small and large dextran molecules through the body is similar to that of PVP. Both are long, slender molecules, with about the same maximum excretable molecular size. The smaller dextran molecules pass rapidly into the urine and diffuse across other capillary barriers, into tissue spaces. Wales (34), analyzing some data of Bloom's, arrived at the conclusion that there is a more or less fixed amount which is required to "saturate" the extra-circulatory spaces or reservoir in the body, and that it takes about 24 hours for this equilibrium to be established. He also found evidence, from blood level and excretion rates,

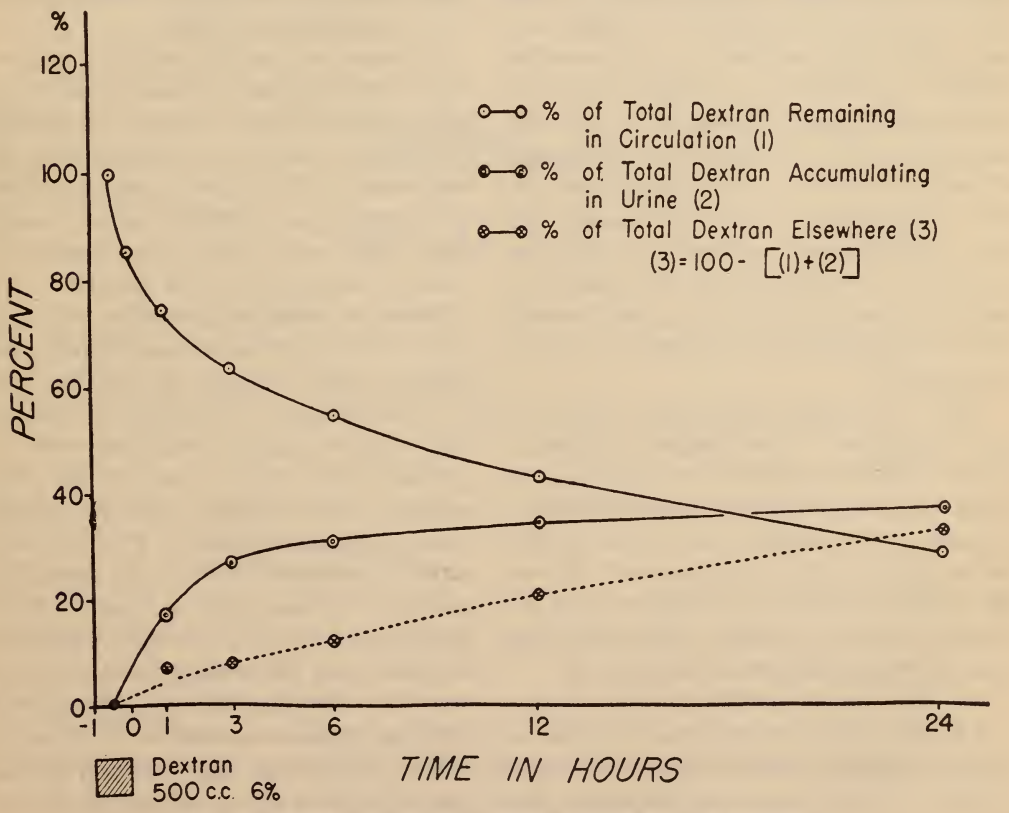

Fig. 6. Plasma Levels, and Urinary Excretion of Dextran.
(From Rousselot and Metcalf (31)).

that there may be an appreciable breakdown of larger dextran molecules into smaller excretable ones, during the course of the 24 hours following infusion.

It is apparent from all this work that in evaluating plasma expanders one has to keep in mind the entire dynamic equilibrium of fluids in the body: not only the circulating blood compartment, but the excretory balance at the renal barrier, and the constant flux into and out of the tissues as well. This is well shown in the recent studies of Mayerson and his collaborators (35), who have been investigating fluid and protein movement in dogs by relating plasma values with the directly measured flow of lymph from the thoracic duct. In their experiments with I^{131} tagged albumin and I^{131} tagged globulin, Mayerson and Wasserman (35) found the following: (1) albumin moves or "leaks" from blood to tissue spaces continuously and quite rapidly, about 1.6 times as fast as does plasma globulin; (2) under normal conditions, it requires 7 to 13 hours for complete equilibrium to establish itself between plasma concentrations, and lymph concentrations; (3) if very heavy doses of albumin are introduced into the blood, equilibrium with tissue fluids occurs much more rapidly—as early as 90 minutes, the albumin flooding out, as it were, the tissue spaces; (4) about one-third of circulating albumin is in the "interstitial" tissue spaces, and two-thirds in the circulating blood.

These interesting experiments reveal an important aspect of the dynamic equilibrium between the circulation and the tissue spaces. There is not only continuing gas and electrolyte exchange at the capillary level, there is continuous protein and water flow as well. Mayerson quotes a statement by Drinker that the primary function of lymph is "the unremitting removal from the tissues of blood protein."

How does dextran perform in this capacity? In a further series of experiments, the plasma-lymph and plasma-excretory relationships were studied by Wasserman and Mayerson (36) after dextran infusions, with the following results: (1) medium to high molecular weight dextran "leaked" only slowly through capillaries, lymph concentration remaining lower than that of plasma for many hours; (2) a low molecular weight dextran, on the other hand, "leaked" rapidly, with lymph concentrations after 30 minutes higher than in plasma, the low value here being due to concomitant loss of dextran through the kidney. By 200 minutes after infusion, all had been excreted, and was in fact recovered in the urine. These relationships are well shown in *Figure 7*.

As a point that may be of some practical interest, we learn from these studies that it is perfectly possible to introduce into the blood stream a macromolecule which remains there more fixedly than the plasma proteins, but there is the question whether this will be at the expense of the normal flow of protein, and perhaps also of fluid, from blood to tissues to lymph and back to blood again. We do not know to what extent, if any, this may be harmful to normal tissue activity.

Of course one can also use hypertonic solutions to sustain plasma volume. This was done in the past with acacia solutions, for treatment of nephrosis, with some success; and has been tried recently with 12 per cent dextran. Except in the presence of peripheral edema, however, there would seem to be no good reason to dehydrate tissue spaces in this manner.

Other physiological properties of dextran and of PVP should be mentioned briefly. After repeated large injections of dextran, Michie (37) noted a drop in Tm-PAH or maximum renal tubular capacity, which recovered only gradually after weeks or months. No clinical evidence of renal damage, however, has been found. Repeated infusions of PVP are also reported to decrease Tm-PAH. No physiological changes have been noted in hepatic function. Both dextran and PVP increase sedimentation rate and there has recently been reported an increase in bleeding time, but there is no evidence at present that either of these is of clinical significance. They are very probably general physical effects of macromolecules in the blood.

Clinically, dextran of accepted U. S. manu-

facture has now been widely used, including some 4000 cases treated in Korea. This experience has been generally satisfactory.

With evidence such as I have given you, on the behavior of blood proteins, and of plasma expanders masquerading as blood proteins, it will be obvious that neither dextran nor PVP is ideal. They both have too wide a range of molecular size. It should be noted that narrower ranges can be obtained, by precipitating out the higher and lower molecular weight fractions but this is an expensive process. PVP is an inert material and is deposited in tissues. Dextran, though metabolized and eliminated, has the tendency common to other polysaccharides of causing antigen-antibody reactions. Both are foreign substances not found in normal human tissues.

We must therefore search further for better expanders. In my remaining time, I should like to review briefly the progress that has been made in developing certain other agents that have shown some promise.

In this evaluation one must first face this question: Why bother with colloid or high molecular weight materials at all? Why not use only crystalloid solutions? As you well know, there is more than a little weight behind this question, and there are those who believe that salt solutions can do all that plasma expanders can. Rosenthal, in particular, has an impressive body of experimental evidence, showing first in mice subjected to thermal burns, later in other animals and with other injuries, that survival can be achieved as well with large volumes of sodium-containing electrolyte solutions, as with plasma or any plasma expander. About three years ago, Dr. Vars (38) and Dr. McCarthy in Dr. Ravdin's laboratory undertook also to re-examine this question. It is difficult to summarize this work in a few words. In fluid replacement studies in bled

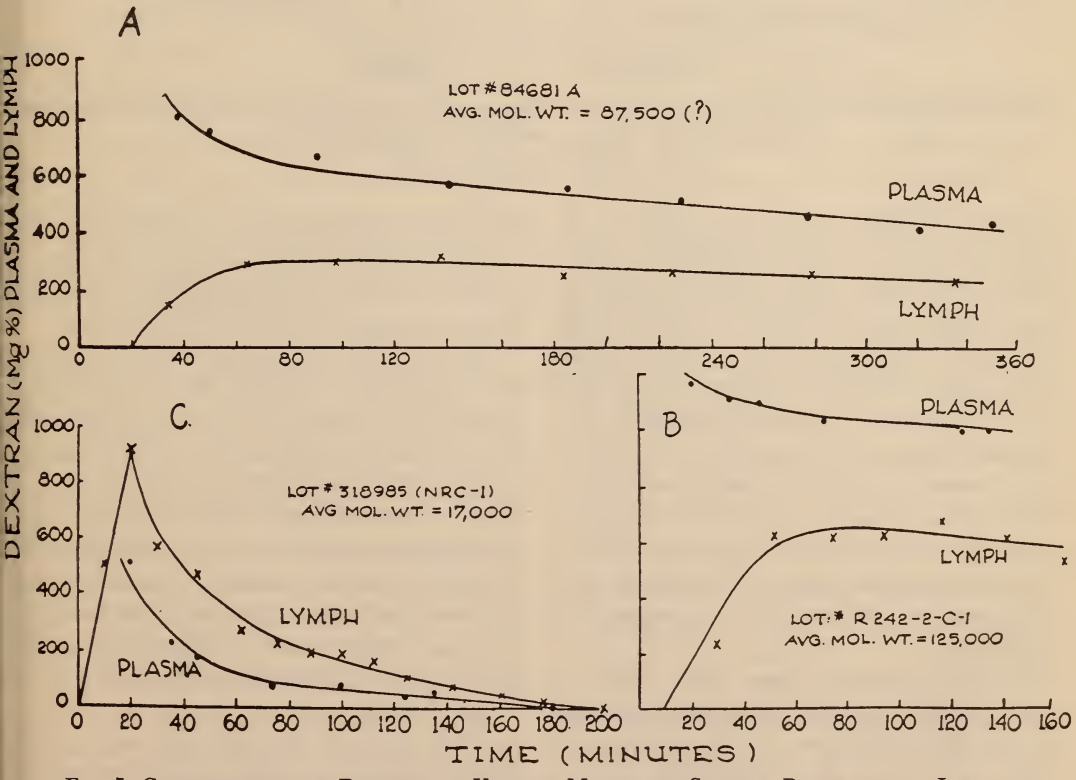

FIG. 7. CONCENTRATIONS OF DEXTRANS OF VARYING MOLECULAR SIZES, IN PLASMA AND IN LYMPH. See text. (From paper by Wasserman and Mayerson (36)).

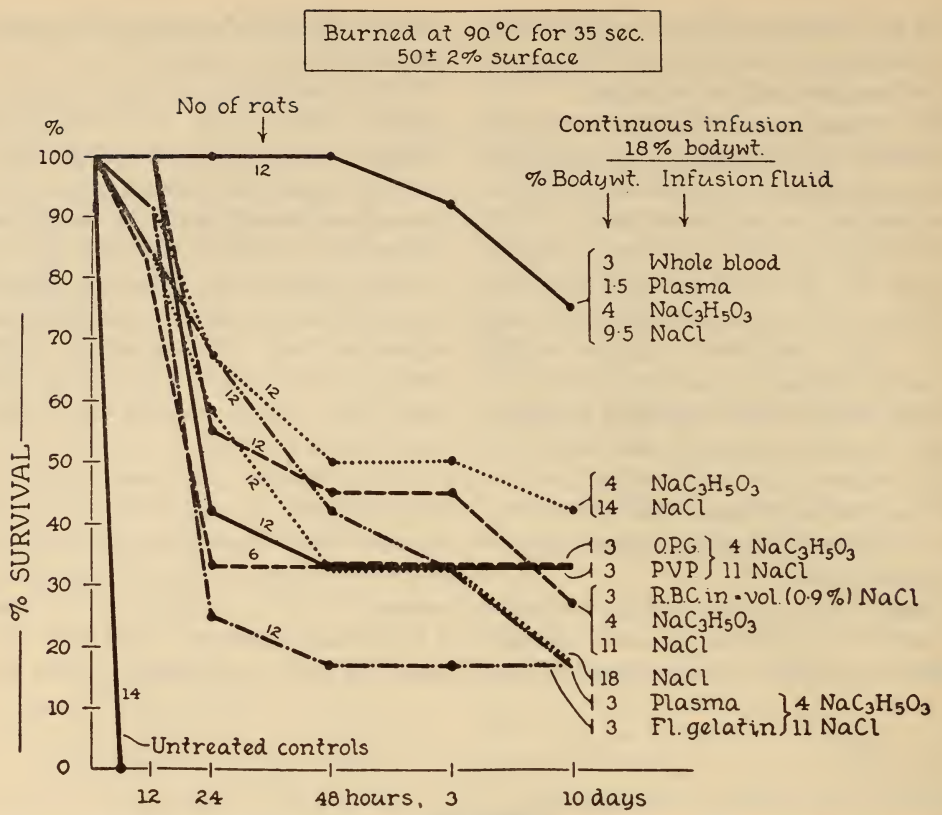

FIG. 8. SURVIVAL IN RATS WITH 50 PER CENT BODY BURNS, AFTER TREATMENT WITH VARIOUS COMBINATIONS OF BLOOD, PLASMA, AND ELECTROLYTE SOLUTIONS.
(From Vars and McCarthy (38)).

dogs, they found that giving saline in an amount twice the volume lost was better than either one or three times the lost volume; too much saline causing excessive tissue edema. An extensive series of experiments with burned rats, treated with large amounts (18 per cent of body weight) of various solutions, in part confirmed the work of Rosenthal, in that crystalloids were as good as plasma expanders. Whole blood, plasma, and saline combined, however, was much better. This is shown in *Figure 8*, from their report. Rosenthal's most recent studies (39) are also consistent with these data.

To what extent do these results apply to man? There is no doubt about the importance of crystalloid solutions in the treatment of injury and shock. The trouble with them as plasma expanders is that they do not expand the plasma; they run right out. I think it is fair to say that those who have seen the most of wound shock are the most emphatic about the failure of saline to sustain the circulation.

It is obvious, but perhaps worth re-stating, that crystalloid solutions, or salt and water, perform one function, and plasma expanders another, each supplementary rather than mutually exclusive. It is the business of salt and water to fill the extracellular spaces, move through them, and to provide an adequate urinary flow. It is the business of plasma expanders to stay in the bloodstream until either blood or plasma can be found to replace them. This is an oversimplification, but I think not too much of a one.

Of the plasma expanders now under study, besides dextran and PVP, those that are furthest along are two modified gelatin prepara-

TABLE 2

COMPARISON OF PLASMA VOLUME EXPANDING EFFECT OF FOUR EXPANDERS

% of Infused Volume (500 cc.) Remaining

EXPANDER	M.W.	TIME (HOURS)					
		0	1	3	6	12	24
Laros dextran...	66,000	110	88	70	61	50	34
C.S.C. dextran...	56,000*	132	87	61	37	29	21
Modified fluid gelatin.....	34,000	91	66	47	34	17	1
Oxypolygelatin...	31,000	74	42	24	15	6	−4

* Average of values by light scattering (68,900), and by end group analysis (43,000).

(From Rousselot, L. M., and Metcalf, W. Progress Report V, N. R. C., 1953.)

tions: (1) Oxypolygelatin, produced by Campbell and Pauling (40) by condensation of gelatin with glyoxal and oxidation with hydrogen peroxide, has a gel point around 18 degrees C.; (2) within the past two years a modified gelatin (41), fluid at 10 degrees C. or lower, has been prepared by Tourtelotte of the Knox Gelatin Company. A 3 per cent solution is isooncotic. The intention with both these gelatins is that they should preserve their plasma-expanding capacity while remaining fluid in the cold. Most investigations with these agents indicate that they are not quite as effective as dextran or PVP, or as whole plasma. *Table 2*, from the studies of Rousselot and Metcalf (42), gives some comparative results.

In this connection, Dr. Ravdin (41) and his associates have questioned the stated criterion of adequacy of a plasma expander—the 12-hour retention of 50 per cent of infused volume—and especially the use of normal subjects as recipients; and this is a fair criticism. It was an arbitrary standard in the first place, as already mentioned. They suggest that a normal person who has been bled a definite amount—such as 1000 cc.—provides a closer comparison with the injured patient. If bled subjects are used, then at once a plasma expander such as modified fluid gelatin gives a much better performance. In their series, for example, bled subjects after 12 hours retained 90 per cent of an infusion of MFG, whereas unbled subjects retained only 10 per cent.

It is difficult to give the right answer to this question. As Ebert (43) has shown, it is largely a question of degree or quantity. The use of normal subjects only provides a more exacting test; a plasma expander must have a greater ability to stay in the circulation when the circulation is normal. Correspondingly, such an agent will do still better in a depleted circulation. It may be that a less effective expander will still be sufficient for most clinical purposes, or that the more adequate expander will serve in some situations, the less adequate in others. Further clinical experience must decide this question.

Many other materials have been tried as plasma volume expanders, and various interesting new ones are under study, such as glucose polymers, and amino acid polymers. It is too early to evaluate these. One can say, however, that there is not as yet any good indication that the ideal artificial expander is just around the corner.

My purpose in this presentation has been to describe the physiological behavior within the animal or human body of certain macromolecular substances of differing composition and varying size, in order to determine if possible what a so-called plasma volume expander should and should not be expected to do. I shall close by an attempt to define this, and the place that an ideal plasma expander should take in the management of the injured patient with blood volume deficit. This statement will doubtless be quite similar to others in the past, but with perhaps one or two new features:

1. A plasma volume expander is of use when a rapid restoration of blood volume is needed and whole blood or a safe human plasma protein preparation is not immediately available. It is essentially emergency or interim therapy.

2. This material should be as nearly as possible homogeneous in molecular size, and such that it will remain in the circulation, with no unfavorable effects, sustaining blood volume for a number of hours, until plasma, or more

especially blood, can be obtained, or until the body can restore its own blood components.

3. The functions of a plasma volume expander will be supplemented by that of crystalloid solutions, as well as by other measures, each to be added separately and as needed.

4. and last. After serving its temporary purpose, the plasma volume expander should be excreted, or metabolized, or both; in other words, it should get out of the way, in favor of returning plasma protein.

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Physicians and Politics in the Revolution: The Case of Adam Kuhn, with a Note on Philip Turpin*

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THIS is the relation of an incident in the life of an early American physician and in the history of the American Revolution. Even to Adam Kuhn, to whom they happened, these events of 1780 were perhaps only an episode; while countless instances of the same kind occurred under the state revolutionary governments harassed by military force and threats to internal security. Yet the story has some contemporary interest; it may even have contemporary relevance.

Born in Germantown, Adam Kuhn studied medicine, first under his father at Lancaster, then in Europe. For a time he was a pupil of Linnaeus at Upsala, and he received his medical degree at Edinburgh in 1767. On his return home the next year, he was immediately elected professor of botany and materia medica in the College of Philadelphia, where his reputation was that of a merely acceptable teacher. The lectures he read were simply those he had heard himself as a student ten years before; he wrote little, if anything, that was original; and was undoubtedly the least important member of the first medical faculty[1].

Like many other Americans of the Revolutionary period Dr. Kuhn seems not to have taken sides strongly in the conflict between England and the colonies. Though his loyalty to the old order was a good deal less than that of a Tory, he was never distinguished for support of the patriot cause as were his brothers. In July 1776 the Council of Safety appointed him physician and director-general of the hospital for the troops then being raised in Pennsylvania to be sent to New Jersey, and presumably he accepted the appointment[2]. But he declined to take the Test Oath of 1777 and as a result was confined to the limits of Philadelphia in July and August. On the other hand, the conflict of loyalties still unresolved in his mind, during these weeks Kuhn identified himself with the citizens of Philadelphia and assured a friend, respecting the impending British invasion, that "we are now determined not to give up to Numbers. . . ."[3] Six weeks later, when Howe's army had come ashore at Head of Elk and was moving overland toward the capital, the Supreme Executive Council of the State adopted several security measures. They directed "that a suitable number of the friends to the Public cause be authorized forthwith to seize & Secure the persons" of some 41 suspected public enemies. On the list was the name of Dr. Adam Kuhn.

The Council, however, was not accustomed to such illegal actions and so, expressing their "wish to treat Men of reputation with as much tenderness as the Security of their Persons & Papers will admit," indicated that some persons should not be confined if they promised in writing "to remain in their Dwellings, ready

* Read before the College of Physicians of Philadelphia, Section on Medical History, 28 January 1954.

[1] On Adam Kuhn, see Marion E. Brown, "Adam Kuhn: Eighteenth Century Physician and Teacher," *Journal of the History of Medicine and Allied Sciences*, V (1950) 163–177; [Samuel P. Griffitts], "Biographical Notice of Doctor Adam Kuhn," *Eclectic Repertory and Analytical Review*, VIII (1818) 235–250; Frank Willing Leach, "The Philadelphia of Our Ancestors," (Phila.) *North American*, Nov. 10, 1907; *D.A.B.*

[2] *Colonial Records*, X, 636.

[3] Kuhn to James Tilghman, Phila., July 17, 1777, in: Carson, Joseph, History of the medical department of the University of Pennsylvania . . . Collection of letters . . . II, 1, College of Physicians of Philadelphia.

to appear on the demand of Council, & meanwhile to refrain from doing any thing injurious to the United Free States of North America, by Speaking, Writing or otherwise, & from giving intelligence to the Commander in Chief of the British Forces, or any other Person whatever, concerning public Affairs." Kuhn gladly gave such assurance and remained unmolested in his house through September, instead of suffering arrest, imprisonment, and exile, which was the fate of those who refused the promise the Council demanded[4].

Probably Kuhn stayed in Philadelphia during the British occupation. But in 1778 or 1779 he left Philadelphia openly for the Danish West Indies. There at St. Croix in May 1780 he married[5], and in the late summer took passage for New York in the sloop *Elizabeth*, Captain William Wesscott, under a flag of truce. Having procured a pass from Admiral Sir George Rodney at New York, the vessel then proceeded to Philadelphia, where it arrived on October 8. Next day the vessel was seized and Kuhn was hailed before the Supreme Executive Council for questioning. That he had sailed directly to New York and had so far acknowledged British authority as to solicit and receive a safe-conduct from them, made Kuhn appear to the Council as "a very suspicious character, whose going at large is dangerous to the Commonwealth." To make matters worse, the *Elizabeth* had affronted the dignity of the Commonwealth as it passed up the river, by not saluting the forts which guarded the approach to the city on the lower Delaware. Kuhn was ordered committed to the new, or Walnut Street, prison, while the vessel's cargo was thoroughly searched for contraband[6].

Three days later, on October 12, the Council relented to the extent of ordering Kuhn and his family to "depart this State in three days" and give security for himself in the amount of £100,000, with two sureties in the sum of £50,000 each, "not to return during this war to any part of America, or to any part of the dominions of the King of Great Britain."[7] What Kuhn may have thought the aggravating consequence of a thoughtless, fearful act had turned into something very serious indeed. He and Captain Wesscott played for time until Kuhn could mobilize his friends.

The *Elizabeth*'s mast was so damaged, Wesscott informed the Council, that he could not put to sea until he replaced it. The Council acceded to his request and lengthened the three days they had allowed Kuhn to one week. The ship and its unwelcome passengers must be away by October 19.[8] As reports of the episode spread through the city, the rumor grew that the *Elizabeth* had carried cargo to the British at New York. Feeling that his own honor was in some measure involved by these rumors, Wesscott went before a justice of the peace on October 16 and swore that he had no interest in the vessel at all and "that no merchandize whatsoever was shipped on board said sloop at St. Croix; and that every article mentioned in the manifest were [sic] brought to Philadelphia, and there stored." That week and the next Wesscott had the affidavit printed in the newspapers[9].

Meanwhile Dr. Kuhn had warned his family of his distress. His brother Frederick hurried down from Lancaster to use his influence to secure a reversal of the sentence of banishment. Frederick Kuhn was described as "a Real Friend to this Country," who not only wished America well but had served as a surgeon in the army until his health required him to withdraw. With him he brought a letter to William Moore, vice president of the Council, from Colonel John Hubley, a respected political figure in Lancaster County. Though admitting that all the facts were not known in Lancaster, Hubley urged the Council to a milder stand.

. . . tho' the Doctr. in his political Character has observed a Line to walk in so as not to take side with either Party in this Contest, which truly is not only very reprehendsible but very unjustifiable, as no Man

[4] *Colonial Records*, XI, 283–284.
[5] Griffitts, *op. cit.*, 239.
[6] *Colonial Records*, XII, 501.
[7] *Ibid.*, 504.
[8] *Ibid.*, 506.
[9] *Pennsylvania Journal*, Oct. 18, 25, 1780.

ought, (let his station of Life be what it may) avail himself of the issue of this dispute (let it turn what way it will) who did not partake of the Toil, risque and danger of it. Yet the acknowledged Abilities of the Doctor in his Profession, his great Use to a rising generation in that way will perhaps induce Council, should his exile be determined on, to continue it only during the War, that he then may return to his Native Country[10]

Before his brother reached town, Adam made his own appeal to Joseph Reed, president of the Council. He had been unable to find bondsmen, he told Reed; the *Elizabeth* had sprung a leak and must stay in Philadelphia some weeks for repairs; Mrs. Kuhn was too ill to go abroad again. But neither Adam's appeals to Reed nor those of his brother to the Council availed anything. With a slight modification, the Council reaffirmed its sentence on October 23. Kuhn was released from the obligation to give £100,000 security that he would not return; but he must leave Pennsylvania in the *Elizabeth* when she was ready to sail in two days; and he was "not to return to any of these United States during the continuance of the present war."[11]

With only hours left before he must quit Pennsylvania, that night Kuhn drafted a final memorial to the Council. Simultaneously his friends prepared a petition to support his. Both papers were laid before the Council on the morning of the 24th.

Kuhn repeated the facts and, without much confidence, renewed his humble prayer:

That your Memorialist arrived at New York on the 23d. of September, in the Sloop Elizabeth, belonging to St. Croix, under a Flag of Truce from the Commander in chief of the danish West india Islands;

That the day after his arrival in New York he desired permission for the vessel to proceed to Philadelphia to land him & his family in this City;

That with much difficulty he obtained this permission on Sunday the first of October (tho dated Septbr. 30th.) and that he left New York on the same day;

That the vessel came solely as a Flag of Truce, and that no trade whatever, either to or from America, was intended.

He declares in the most solemn manner that the above is a true state of facts, and that he took this method of returning to his native country, by the advice & at the desire of his Father in law, Isaac Hartman Esqr., to secure his family and property against depredation and capture from british Cruizers.

Your Memorialist acknowledges his great imprudence in the manner of his return, which proceeded altogether from an error in Judgment, without the least intention on his part to violate or infringe the laws of his Country.

He therefore earnestly requests the honourable supreme executive Council, to take his case once more under consideration, and to grant him such indulgence as may be thought consistent with their duty to the commonwealth; but if it should be deemed indispensably necessary for your Memorialist to depart in the vessel for St. Croix, he prays to be favoured with leave to return in the Spring and that he may not be constrained to continue in Exile during the war.

It having been suggested to your Memorialist that he was deficient in due respect to the Garrisons below the City, he embraces this opportunity to declare, that he is extremely sorry for any omission on his part; but he begs leave to assert his innocence to the honourable Council in this instance; as the Pilot, to whom he applied for information, assured him that it was not usual for Vessels to bring to at the Fort, or to shew Colours before they turned Gloucester point[12].

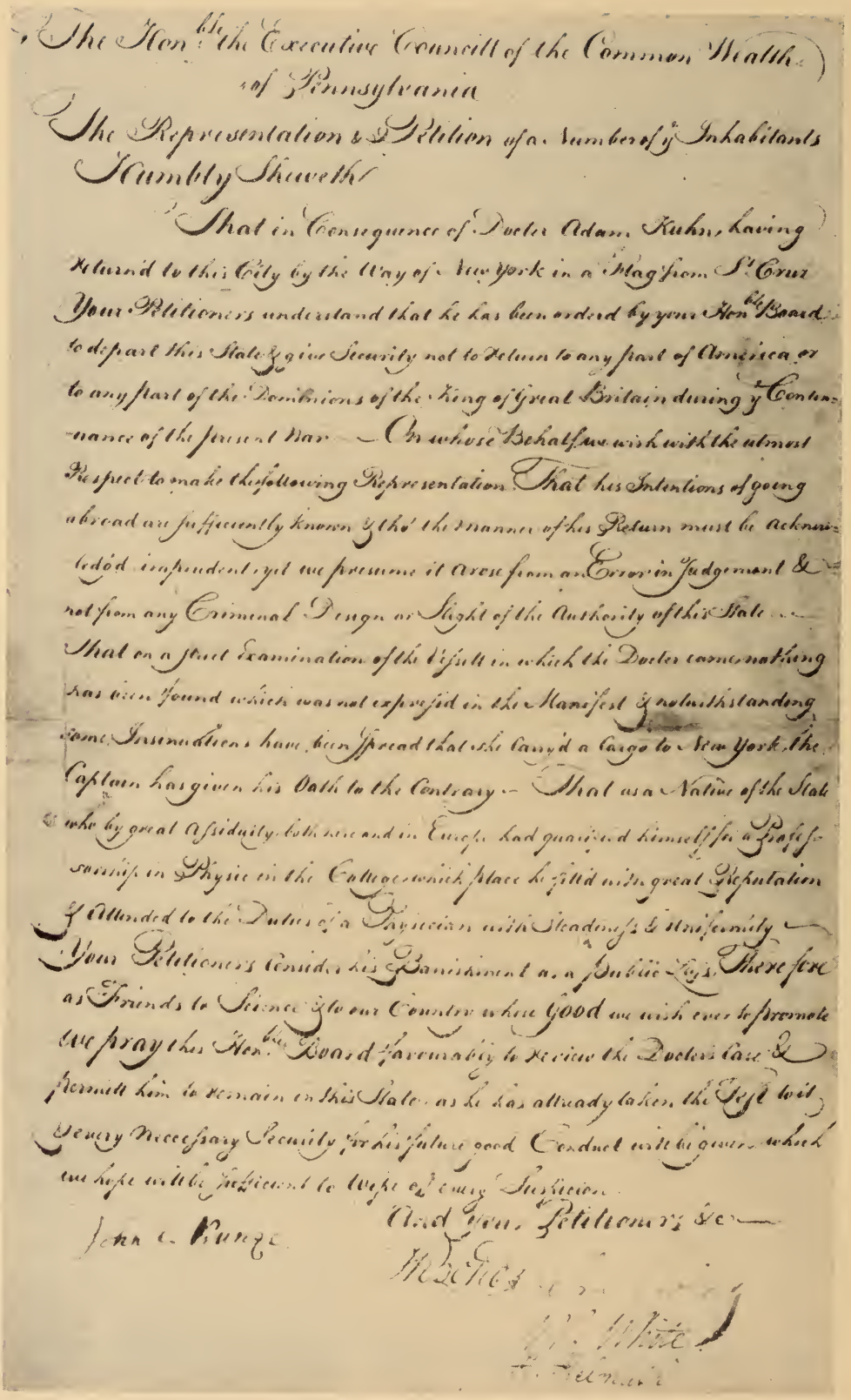
The supporting petition of Kuhn's friends (*Fig. 1*) was signed by 48 citizens of Philadelphia. His colleagues of the medical faculty, led by Thomas Bond, all signed; so did the Reverend Mr. William White, the German ministers Henry Helmuth and John C. Kunze, Provost John Ewing of the University of the State of Pennsylvania, Captain Nathaniel Falconer, and merchants like Lawrence Seckel, Jacob Hiltzheimer, Christopher Marshall, Jr., Henry Keppele, and Samuel Wetherill, Jr. The petition asserted that Kuhn's intentions in going to the West Indies were widely known and that though the manner of his return was imprudent,

yet we presume it arose from an Error in Judgement & not from any Criminal Design or Slight of the Authority

[10] John Hubley to William Moore, Lancaster, Oct. 14, 1780, Revolutionary Papers, XL, 20, Pennsylvania State Archives, Harrisburg; printed in *Pennsylvania Archives*, ser. 1, VIII, 586.

[11] *Colonial Records*, XII, 516.

[12] Revolutionary Papers, XL, 29, Pennsylvania State Archives, Harrisburg.



To the Hon.ble the Executive Council of the Common Wealth of Pennsylvania

The Representation & Petition of a Number of y.e Inhabitants

Humbly Sheweth

That in Consequence of Doctor Adam Kuhn having returnd to this City by the Way of New York in a Flag from St Croix Your Petitioners understand that he has been ordered by your Hon.ble Board to depart this State & give Security not to return to any part of America or to any part of the Dominions of the King of Great Britain during y.e Continuance of the present War — On whose Behalf we wish with the utmost Respect to make the following Representation That his Intentions of going abroad are sufficiently known & tho' the manner of his Return must be acknowledgd irregular yet we presume it arose from an Error in Judgement & not from any Criminal Design or Slight of the Authority of this State — That on a strict Examination of the Vessell in which the Doctor came nothing has been found which was not expressd in the Manifest & notwithstanding some Insinuations have been spread that she Carry'd a Cargo to New York the Captain has given his Oath to the Contrary — That as a Native of the State who by great Assiduity both here and in Europe had qualified himself for a Professorship in Physic in the College which place he filld with great Reputation & Attended to the Duties of a Physician with Steadiness & Usefulness — Your Petitioners consider his Banishment as a Public Loss Therefore as Friends to Science & to our Country whose Good we wish ever to promote We pray this Hon.ble Board favourably to review the Doctors Case & permitt him to remain in this State as he has already taken the Test will Security necessary for his future good Conduct will be given which we hope will be sufficient to Wipe off every Suspicion

And Your Petitioners &c —

John C. Cruze

W. Bell

W. White

F. Belmain

FIG. 1(*a*). THE PETITION SIGNED BY THE MEDICAL FACULTY AND OTHER PROMINENT CITIZENS OF PHILADELPHIA ON BEHALF OF ADAM KUHN.

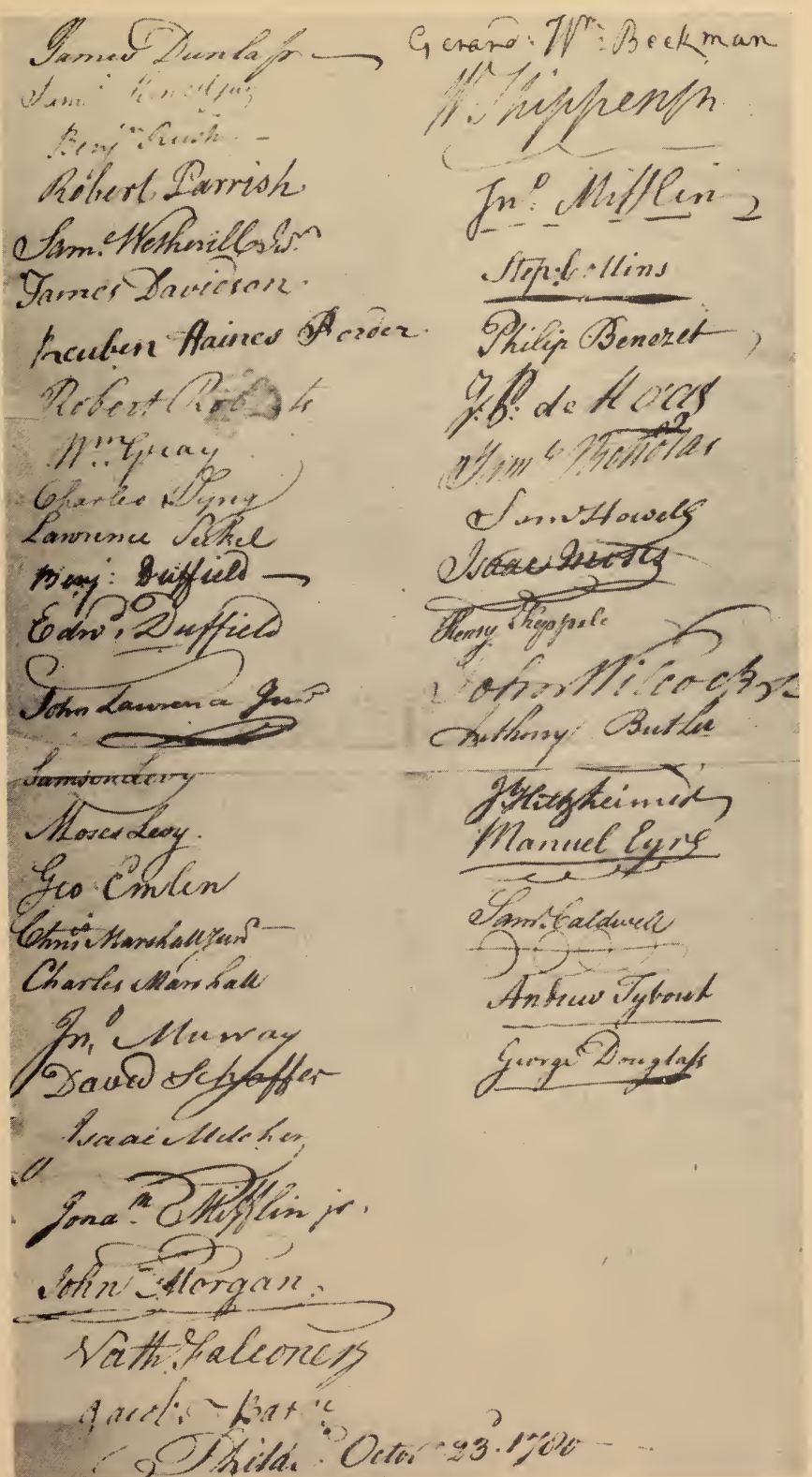


FIG. 1(*b*). *Continuation of Fig. 1(a).*

of this State. That on a strict Examination of the Vessell in which the Doctor came nothing has been found which was not express'd in the Manifest & notwithstanding some Insinuations have been Spread that she carry'd a Cargo to New York the Captain has given his Oath to the Contrary. That as a Native of the State who by great Assiduity both here and in Europe had qualified himself for a Professorship in Physic in the College which place he fill'd with great Reputation & Attended to the Duties of a Physician with Steadiness & Uniformity—Your Petitioners consider his Banishment as a public Loss. Therefore, as Friends to Science & to our Country whose Good we wish ever to promote, we pray this Honble. Board favourably to review the Doctor's Case & permitt him to remain in this State, as he has allready taken the Test to it, & every necessary Security for his future good Conduct will be given which we hope will be sufficient to wipe off every Suspicion[13].

The Council read Kuhn's memorial and rejected it. A clerk made a notation on his friends' petition that it too had been "read & rejected." The next day the *Elizabeth* sailed from Philadelphia for the West Indies with Kuhn aboard as a reluctant exile from his homeland.

The arguments Kuhn's friends and relations used are interesting to find urged in the middle of a struggle which had many features of a civil war. To the question whether a citizen's civil contributions to the state can outweigh immature and even equivocal political conduct, they gave an assured affirmative. That they were not alone in their opinion, that others believed it was desirable, even necessary, sometimes to draw a veil silently over such political indiscretions as Kuhn's, the case of Dr. Philip Turpin of Virginia clearly demonstrates. The facts were these:

Young Turpin went abroad to study medicine. After receiving his degree at Edinburgh in 1774, he crossed to France to visit the Paris hospitals. Returning to London in the spring of 1776, intending to take passage for America, he found that all remittances from Virginia had been cut off, and he was without funds. For 15 months he lived on the charity of friends in the country. In the fall of 1777, still without funds, he went up to London where he tried vainly to borrow passage money from merchants who knew his family. Without funds or friends in London, with no other resource than his profession, Turpin took a berth as a surgeon on a stationed vessel of the Royal Navy. He hoped in this way not only to provide for his present subsistence, but to save enough to pay his passage home. Accordingly, when he had enough for that purpose, he left the ship for London; after six months, still unable to get passage and once more without means of support, he returned to his former berth aboard the vessel. Finally in the spring of 1781 Turpin at last obtained passage on a military transport for New York, on condition that he serve as surgeon. The ship put in at Charleston; failing to find a replacement for himself, though he advertised in the papers, Turpin accompanied the vessel to New York, as he had agreed. There he took the first opportunity to get to Virginia, which he did by ship in the summer of 1781. But Turpin was landed in British-held Virginia. Lord Cornwallis refused him a pass back to the American lines; and so, a civilian physician, unable to secure food or quarters, Turpin took a post in the British military hospital; and in this capacity he was serving when Cornwallis surrendered his army. Governor Nelson of Virginia was satisfied with Turpin's statement of his unlucky career and gave him a passport to return to his friends.

A year later, in October 1782, the Virginia Assembly enacted a law against its citizens who had borne arms against the Commonwealth during the war. Alarmed for his future safety, Turpin consulted his cousin Thomas Jefferson, who prepared a long review of the facts and the law in the case.

The basic question, Jefferson declared, was what Turpin's *intent* was. At no time, he found, did Turpin ever *intend* to assist the British; on the contrary, every action was the result of absolute necessity to obtain present subsistence. "Force or fear will justify the furnishing an enemy with provisions, with money, with arms, ammunition &c. This has been the predicament of a great part of the citizens of

[13] *Ibid.*, 27.

America. They will in like manner justify the joining an enemy and bearing arms against one's country. . . . This was the case of our citizens taken captive on the high seas. The peculiarities in the late war have produced many new and trying cases. . . ." Jefferson went on to cite the case of American soldiers captured at Fort Washington, Long Island, and Charleston, who enlisted in the British army in order to obtain an opportunity to escape to the American lines. Until that opportunity offered, they actually bore arms against their countrymen. Turpin's case, Jefferson thought, was not unlike theirs, except that they had a claim on their jailers for subsistence and on their country for exchange, while he had no support except his profession and no way to get home but by his own exertions. If Turpin's reasons for entering the British service seemed less urgent than the prisoners', yet the means he chose—by administering to sick and wounded —were less offensive. ". . . your plan of escape was by saving the lives of enemies while theirs was that of taking away the lives of their countrymen. The office of surgeon has been considered as on a footing with that of chaplain, and the administering of medicine to be as inoffensive as giving religious instruction to those with whom we are contending."

If the term "bearing arms" was broadened to include those who did so with innocent intent, like the Fort Washington prisoners, and those who out of fear rendered other services, like furnishing the enemy provisions, transporting their baggage, and serving them as guides, then, Jefferson concluded, "it must sweep off a number of our very good citizens. . . ."[14]

Happily Adam Kuhn was not "swept off." The four Kuhn brothers—John, Frederick, Peter, and Jacob, patriots all—rallied to their luckless brother's cause. On March 5, 1781, they presented their fraternal memorial to the president of the Council. Before he left Philadelphia, they assured the Council, Dr. Kuhn "express'd his anxious Desire to reside in this, his Native Country, by several respectful applications to your Honble. Board, for Permission to remain here, as also at his Departure left Directions with us, to interfere on his Behalf & since his Residence at St. Croix, has inform'd your Memorialists, that the Climate is so injurious to his Health, that of Necessity he must leave it, and is therefore exceeding Anxious to return to this City."[15]

The petition was read in the Council on March 7. A request by the Kuhns of Lancaster was not lightly to be denied; besides, the doctor's health might actually be in danger from the tropical climate; and, furthermore, the honor and dignity of Pennsylvania had been vindicated. The prayer of the petition was accordingly granted,[16] and in the summer of 1781 Dr. Adam Kuhn returned to Philadelphia.

He taught and practiced there for more than 30 more years; engaged in noisy professional quarrels in the tradition of 18th century medicine; was elected president of the College of Physicians; and died at last in 1817, not viewed with reserve or hostility as a "suspicious character" because of the *Elizabeth* affair, but hailed as an eminently valuable citizen of his country.

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[14] Jefferson to Turpin, Monticello, July 29, 1783. Julian P. Boyd and others, eds., *The Papers of Thomas Jefferson* (Princeton, 1950—), VI, 324–333. I am indebted to Dr. L. H. Butterfield for calling my attention to this letter.

[15] Revolutionary Papers, XL, 29, Pennsylvania State Archives, Harrisburg.

[16] *Colonial Records*, XII, 650.

Presidents' Gavel—Presentation Speech

By GEORGE E. PFAHLER, M.D.

3 March 1954

President Richard Kern, Fellows of The College of Physicians, and Guests:

I thank you for this opportunity to express to you my deep appreciation of the many courtesies and great kindnesses that have been shown to me by you, my colleagues, both individually and collectively. The College of Physicians stands at the top of the medical organizations in this city, and it is a great honor to be made a Fellow. I am fortunate in being one of the oldest living Fellows, and, therefore, I have had the privilege of seeing the accomplishments of this organization and have recognized the usefulness of its great Library. I have never been honored with the Presidency but those who have served in this great office comprise the names of many of the greatest leaders of medicine in this country, and they are men whose names and memories must always be an inspiration to us and to those who follow us.

It occurred to me it would be an inspiration for every incoming President to have before him constantly the names of the Past Presidents. For this reason, I have had the names of all Past Presidents engraved on a silver plate on the top of this box with space for the engraving of the names of future presidents during the next 100 years. I am hoping that this gavel may be used routinely.

The Gavel which this box encloses is a remnant of one of the oldest and largest creatures that has lived on this earth. It is made of Mastodon Ivory obtained in Alaska. The Mastodons in Alaska were present in the Pleistocene Period, probably more than 25,000 years ago, when Alaska had a tropical climate. Some of these Mastodons became mired in the mud and the bones were fossilized, then covered with glaciers as the cold period followed, then were buried in the ice during the Glacial Period. These tusks are now being discovered in the melting glaciers. The many thousands of years have produced in this fossilized ivory beautiful colors which are not present in the ordinary ivory obtained in modern times. This age-old and former living tissue which has been preserved over this long period should serve as an emblem of the durability of the work of our great physicians.

I have always looked upon the medical profession as the greatest fraternity in the world, and I am making the presentation of this Gavel and these records as a token of my appreciation of the privilege of being a member of this great fraternity.

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The Treatment of Arterial Hypertension*†

By IRVINE H. PAGE, M.D.

I AM most grateful for the privilege of delivering the Hatfield Lecture and for the pleasure of seeing many of my old friends in Philadelphia. That pleasure has hardly been lessened by the preceding Lucullan dinner. I wish I were able to return an intellectual feast in kind.

The story I have to tell is one of continuing endeavor; we no longer treat hypertensives with enforced vacations, "individualized" nursing care and masterful expectancy; unfortunately our mastery is still incomplete. Many of the agents now employed are useful but most of them have their dangers. Twenty-five years ago the agents used seriously by physicians—mistletoe, watermelon seed, garlic, whiffless garlic, and a host of weird and wonderful concoctions were, at least, not dangerous even if they were not vasoactive. I think it not bold to predict that now that interest has at last been aroused, new drugs and chemical modification of older ones will appear with fair rapidity.

To me the most impressive single achievement in recent years has been the demonstration that the syndrome of malignant hypertension can be reversed, usually to pre-existing essential hypertension. Early in my career I was greatly impressed with the lethal character of malignant hypertension. It was only the rare patient who did not die within a year or two. Then came sympathectomy; we did the old anterior nerve root section through a "yard" long laminectomy. But for the first time in 1933, I saw the malignant syndrome reversed in several of my patients. I know few believed it at the time; doctors, especially the surgeons and internists, were too busy defending or impugning the operation or each other.

Then came kidney extracts with all their difficulties: again we saw reversal of malignant hypertension and were met with disbelief. I still do not know for sure whether or not kidney extracts contain anything but pyrogen. I am pretty sure that they do, which may merely show how stubborn I am. For instance, we are now working on an extract that blocks the pressor action of angiotonin and renin. When injected into a nephrectomized dog it prevents the increased responsiveness to vasoactive drugs which is a normal sequel to nephrectomy. In any case, kidney extracts did produce fever in many patients. Later when soluble bacterial pyrogen became commercially available, we undertook for the third time the treatment of the malignant syndrome

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† From the Research Division, Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

with considerable success. Nowadays there are easier ways of achieving much the same results.

I have mentioned these endeavors because it is illustrative of what I think will happen with other aspects of treatment. The reason I see no reason to worry about working ourselves out of a job is that we have scarcely begun with the specific treatment of hypertension based on its varied mechanisms; when that is achieved the really major problem of arteriosclerosis will still be available.

It has been increasingly evident that the drugs we have are definitely helpful in only a minority of the patients and that each drug helps a different, albeit unidentified, group of patients. Roughly the percentages run 20 per cent arterial pressure reduced to normal, 30 per cent helped definitely, 20 per cent possibly, and 30 per cent not helped at all. After the appearance of each new remedy, the natural history follows pretty much through a routine cycle: it is the miracle drug, it then is discarded as almost useless; the final evaluation yields roughly the percentage distribution I just mentioned. And I hasten to add another and even more important point; no one knows how to select the patient who will respond.

I have never tired of saying that if we could select the 20 per cent of hypertensives who get a fine result from sympathectomy, there would be no doubt about the place of this operation in the management of these diseases. But for years we have told ourselves, "If the patients are well selected the results are good," but we have carefully avoided disclosing how to select patients "well."

Arterial hypertension, to me, is a multifaceted disease of multiple etiology. It is obvious that it is associated with such diverse conditions as chronic glomerulonephritis, adrenal carcinoma, carcinoma, pheochromocytoma and poliomyelitis. What is not so evident is that what seems to be ordinary essential hypertension probably also is of multiple etiology.

If one thinks of the various systems in the normal body which control blood pressure, it is possible to divide them into renal, endocrine, nervous and cardiovascular panels. Experimental manipulation of the kidneys is well known to produce hypertension, and clinical examples of the association of renal disease and hypertension are abundant. No special pleading is required for the endocrine glands; indeed, for a while it looked as though the adrenal glands had gotten completely out of hand and through their participation in stress and adaptation threatened to be the cause not merely of hypertension, but nearly everything else.

Hypertension of a very severe grade can be produced in animals by section of the buffer nerves and this is clearly of neurogenic origin. Indeed, when this occurs, the response of the blood pressure to a variety of drugs is radically changed. For instance, as compared with a normal dog or with one having renal hypertension, the response to tetraethylammonium chloride is entirely different in the neurogenic hypertensive. Just so, a few patients also exhibit this altered pattern of response, suggesting that in them the hypertension might be primarily of neurogenic origin associated with alterations in the buffer nerves. For the past 5 years we have been trying to unravel this complex problem of mechanism in both patients and animals with hypertension of known etiology by the pharmacodynamic approach. Naturally, we hope it will provide a method of selecting patients objectively from the large group of both the essential and malignant varieties.

Currently, then, there are no objective criteria for selection and all that can be done is to test each drug for its efficacy in the patient. And here I should add the warning that we are entering on a new age of polypharmacy. Pills are now being sold with every sort of mixture in them, making appropriate individual use of the drug and adjustment of dosage impossible. These shotgun mixtures have no place in rational therapy; they are the lazy man's placebo.

Some patients respond to hydralazine, some

to hexamethonium, some to reserpine, a few to the veratrum drugs, and so on. The other side of the coin is that a very large number of them who respond to one show no effect from another and that some respond to none. To give a drug while getting no good from it is not only costly but runs the long term risk of experiencing its bad effects without the saving grace of the good.

I see no objection whatever to the utilization of multiple drugs to affect multiple mechanisms but these mechanisms have to be recognized, if only by showing that a particular drug is effective before another one is added. The orderly testing of various treatments and their rejection when they prove wanting is a very necessary condition not only for the experimental analysis of the problem in patients but for intelligent treatment.

REVIEW OF CURRENT METHODS

1. *General Measures.* Treatment with drugs is not good enough to allow physicians to discard those measures which transfer the load of chronic illness to the shoulders of the physician. The cultivation of equanimity, the orderly readjustment of the stresses of life, and the many other changes producing a life of moderation and happiness do not cease to be a mainstay in treatment. Arterial hypertension is a very chronic disease; the patient must be educated to live with it.

2. *The Search for Causes.* The searching out of the common definable and the more obscurely recognizable causes of hypertension continues to yield a sizable complement of patients masquerading as essential hypertensives: who, because the true origin of their illness is overlooked, have not reaped the benefit of highly specific therapy. Pyelonephritis is still better treated with antibiotics than hexamethonium, and coarctation of the aorta seems more logically cured by cutting it out than by hydralazine.

3. *Diet.* Only 10 years ago we endured the period of intensive dietary treatment of hypertension. Bizarre diets of all sorts were being recommended with fanatical assurance. It seems to have come down to this: about 25 per cent of patients respond with a fall in pressure almost to normal when on a strict low-salt diet, i.e., one that yields less than 200 mg. daily. The rest show either no effect or a very moderate one. No method for selecting susceptible patients has been found. Whether one wishes the psychic mortification of the "rice" diet or the dubious gratification of a planned low-salt diet, is up to the individual. So many good low-salt diets and foods are now available that there is no necessary recourse to the "rice-house." A reliable wife is one of the most useful and often essential adjuncts to a strict low-salt diet.

4. *Potassium Thiocyanate.* This drug still has its place, in my view, in patients with intractable headaches. Often these can be relieved by single intravenous injection of 1.0 gram of thiocyanate ion. If the blood thiocyanate level is kept at from 3–6 mg./100 ml., often the headaches will not return. Combinations of small doses of thiocyanate and phenobarbital are sometimes especially effective. Thiocyanate also has a moderate hypotensive action. Some sedative effect is noted by most patients. It is a drug to be used with discrimination and the blood level should never go unmeasured for long periods of time.

5. *Veratrum.* Our results with the veratrum alkaloids, whether as mixtures or the pure drugs, show only a small number of patients exhibiting impressive responses. In many the hypotensive and emetic doses are so close that use of the drug is impractical from the start and in most these overlap as time goes on. The lesser hypotensive effects have seemed too insignificant to justify the use of such expensive drugs. Occasionally patients with severe hypertension show an almost specific response but these are not common in our experience. We have had little interest in treating patients in the very early stages of hypertension with this drug. In fact, most of the drugs available are potentially too dangerous for use in the early phase of the disease, unless vascular disease is advancing at a measurable rate.

6. *Sympathectomy.* I think most would agree that about 20 to 25 per cent of patients operated upon show moderate to marked improvement. The rest show varying grades of it. If a method of selection were found which would convert the 20 per cent to 95 per cent, there would be no doubt about the place of the operative treatment of hypertension. Theoretically, patients with a high degree of nervous tone should respond best and this may be demonstrable by recording the pattern of response to TEAC and to serotonin. Unfortunately these tests are still in the process of validation and cannot be recommended for routine use. Also, according to theory, a total sympathectomy in such patients should be performed because of the observation that an incomplete sympathectomy in dogs with neurogenic hypertension is ineffective in lowering arterial pressure.

7. *Adrenalectomy.* My talks today with my old friend William Jeffers have convinced me that total adrenalectomy has a limited place in the treatment of severe hypertension. It should be limited to patients with enough intelligence to recognize symptoms of adrenal insufficiency, enough money to secure the means of its control and cure, to those who are close enough to a team of trained and constantly available workers and, finally, those who understand the nature of their problems. The results in some patients are excellent but like all treatment so far, there are enough failures. This is not the place to discuss this work in detail. I am delighted that the problem is in thoroughly competent hands here in Philadelphia. It will take several years more study to define the position of adrenalectomy in therapy, alone as done by Jeffers, and adrenalectomy with sympathectomy, as done by Wolferth.

8. *Pyrogens.* I mention them again chiefly to keep the problem of their use alive. When we had little else to reverse malignant hypertension, we were very glad to use daily treatments with injectable pyrogen. Some of the results were as good, or better, than anything we have today, but of course the treatment was rugged, and the ultimate mortality high.

I believe the pyrogen problem has been entirely inadequately studied. It is not known whether pyrogenicity and the favorable effects on vascular disease parallel one another. It is possible that the fever production is not at all necessary to heal the necrotizing arteriolitis. The first thing needed is a serious minded chemist to study basic chemical structures without trying to get a product to sell. A course of pyrogen followed by hydralazine or hexamethonium or both may have much to recommend it provided renal function is not too low (<35 per cent urea clearance).

9. *Hydralazine* (*Apresoline*). This drug is not an easy one to use if its full benefit is desired. Dosage varies greatly from patient to patient; the effective range seems to be 200 to 700 mgm. daily. When it is started, the patient may have a period of several weeks during which headache, anorexia, nausea, flushing, palpitation, edema and even fever may cause discomfort and alarm. He may feel he is getting pyrogen spelled backward. Reassurance and persistence in treatment will bridge this sometimes unhappy period. After a fully effective dose has become established, it should be slowly reduced to the minimum which will maintain the hypotensive effect.

With full doses about one quarter of the patients will respond by decreases of diastolic pressure to normal, a third by a decrease of pressure to less than 110 mm. Hg and the remainder show moderate or no effect. Again it is seen that while beneficial in many patients, by no means all respond, either with a fall in blood pressure, or betterment in the vascular disease. Favorable responses have now lasted for 3 years in our experience.

We have the clinical impression that the best responses occur in patients in whom the disease seems, on hunch, predominantly of "neurogenic" origin; this is an example of the utter inadequacy of current knowledge of mechanism.

Some of our patients who have taken hydralazine for a year or more have shown a most remarkable syndrome clearly associated with the drug. In its milder form it resembles early rheumatoid arthritis, and in its severer form, simulates most aspects of severe acute systemic lupus erythematosus. The syndrome usually disappears on withdrawal of the drug or even on reduction of the dose. Cortisone has been helpful in the management of the lupus-like form in a few of the patients.

The mean time of onset of this complication was one year after starting hydralazine and the average maintenance dose 640 mg. daily. Our severity index[1] ranged from 2.2 to 9.6, hence severity did not determine the onset. The most desperately ill patient scores 16. The most characteristic laboratory changes were decrease in serum albumin and increases in alpha and gamma globulins—a most unusual electrophoretic change indeed.

The initial rheumatic state may be succeeded after varying intervals by a syndrome of fever, prostration, chest and abdominal pain and signs of acute systemic lupus. One patient out of five showed a positive L. E. test in the plasma and one a positive test in the bone marrow. Arterial pressure is greatly reduced during this phase. It has seemed to us that this is an induced collagen disease well worth careful study by the "ground substance boys."

10. *Hexamethonium.* This drug acts by partially blocking transmission of nervous impulses in both sympathetic and parasympathetic ganglia. It is strongly anticholinergic. Fall in blood pressure, especially of the postural sort, is only one of the signs it produces. Others consist of dilatation of the pupil, dryness of the mouth, bladder atony, constipation, or diarrhea.

[1] A composite assembled from four panels, namely, arterial pressure and the status of cardiac, renal and cerebral functions; each graded 1 to 4. The index has been described in detail (Taylor, Dustan, Corcoran, and Page, 1952). It is much more inclusive than the usual methods for clinical grading of severity.

There is no doubt hexamethonium is initially effective when given intravenously or intramuscularly in most patients. Some are refractory from the start or may soon exhibit marked increase in tolerance (*Fig. 1*). A rest period of several days often restores sensitiveness. Absorption by mouth is probably not more than 5 per cent efficient and in many patients irregular. But some patients do quite well when given it this way, especially early in treatment before tolerance has developed; many do not.

I think the drug must be given and adjusted much like insulin when treating patients with severe vascular disease. Quick and effective treatment usually can thus be insured. We employ the low-salt diet along with it largely because most of our patients requiring this sort of treatment are bordering on cardiac failure. We also like to take advantage of postural hypotension by use of the head-up bed.

Many of the side effects such as bladder atony can be overcome, at least partially, by use of Urecholine or Myastenol. Urecholine is a strong parasympathetic stimulator not destroyed by cholinesterase. We have used it for some time by mouth in doses of 5 to 20 mg. two or three times a day. The effect may not last longer than an hour. It is not to be given intravenously or intramuscularly. Careful control of bowel action must be kept. Even more important is teaching the patient how to avoid or correct postural hypotension.

Combinations of hexamethonium and hydralazine may be helpful in patients responsive to both drugs (*Fig. 2*). Hexamethonium may prevent tachycardia in the early stages of hydralazine treatment. So far, we have uncovered no evidence of a true synergism between the two drugs; the concept of synergism has been widely accepted without proof.

Hexamethonium will never be an easy drug to use. We have had some success in adjustment of dosage by teaching the patients to take their own blood pressure at

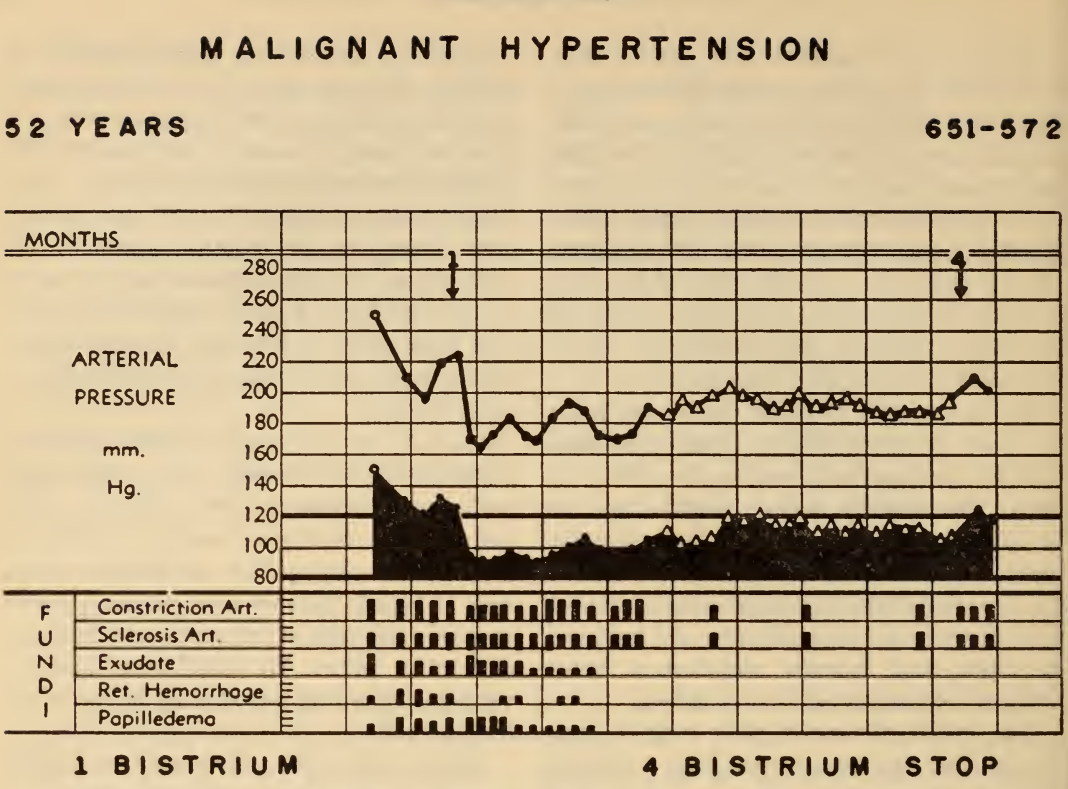

FIG. 1. Demonstration of the development of tolerance to hexamethonium. At (1) hexamethonium started and stopped at (4.) Each dot on the blood pressure chart is an average of one week, pressures being measured in the morning and evening. Eyeground examinations are graded on a 1–4 basis. Vertical lines represent months.

home, and changing the dose according to the pressure readings. We can hope that a drug will be developed which blocks sympathetic but not parasympathetic impulses—an improbable hope when dealing with the acetylcholine mechanism of transmission.

11. *Rauwolfia—Reserpine.* The vasoactive alkaloid from the usual type of Indian Rauwolfia on the market is reserpine; much the same results seem obtained by less purified extracts of the plant, though dosage is uncertain. In dogs, reserpine elicits a peculiar type of stupor in which the animal remains very quiet but can readily be roused. It certainly differs from the type caused by barbiturates.

We have usually employed the drug with those patients in whom a high degree of neuromuscular excitability has been evident. It makes many patients sleepy, which is usually desirable. It usually produces nasal congestion. In the early stages of the disease, when it is very questionable whether any of the available drugs are needed, reserpine seems to reduce arterial pressure effectively in some patients. As the disease becomes more severe it becomes far less effective. A period of 3 weeks is usually required to demonstrate its effectiveness, or lack of it.

An occasional patient shows an almost specific response to the drug; arterial pressure may fall completely to normal after years of sustained hypertension which has failed to respond to the other usual anti-hypertensive drugs.

The drug probably is contra-indicated in the presence of severe renal insufficiency. We have seen an almost pure Parkinsonism elicited by reserpine in the terminal stage of Bright's disease. Occasional patients show some mental disturbance, especially severe depression. Extreme fatigue with severe depression is

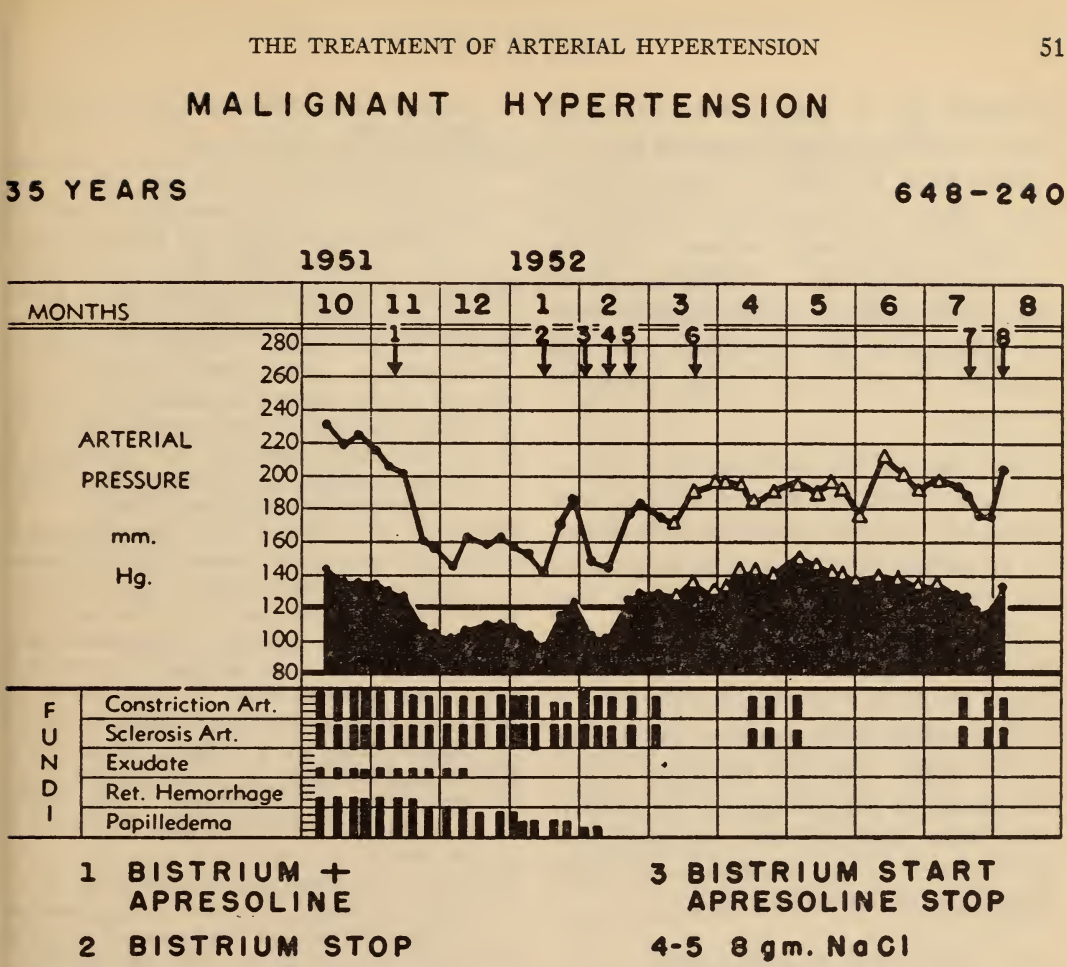

FIG. 2. Combined treatment with hexamethonium and hydralazine in a patient with malignant hypertension on a strict low-salt diet. At (1) hexamethonium and hydralazine were started; (2) hexamethonium stopped with rise in blood pressure; (3) hexamethonium started and hydralazine stopped with fall in arterial pressure; (4)–(5) 8 grams of salt added to the diet with rise in blood pressure; (6) hexamethonium discontinued.

probably the most common symptom of either overdosage or undesirable side effect.

We have employed doses ranging from 1 to 10 mg. a day, but gradually have given up the higher doses; the average is now 1 to 2 mg.

12. *Sodium Nitroprusside.* I pointed out several years ago that this drug might be conveniently and very cheaply employed for controlling the level of blood pressure when given by intravenous infusion. In animals it is a very powerful depressor agent, acting almost exclusively on the peripheral vessels and dependent on the nitroprusside ion remaining intact. It seems to have little direct effect on nervous control of blood pressure.

We make up a stock solution of ordinary reagent type sodium nitroprusside in a concentration of 2.5 mg./ml. It is sterilized by filtration through a Seitz filter and then is ready for dilution when needed.

When given at a rate of from 50 to 100 micrograms/minute, arterial pressure can be kept at almost any desired level. On discontinuing the drug it promptly rises. We have uncovered no evidence of tolerance. Ganglionic blockade with tetraethylammonium or hexamethonium in dogs clearly shows augmentation of its depressor action; in patients hexamethonium also augments it.

For the control of hypertensive encephalopathy the drug is eminently suited. By increasing or decreasing the infusion rate, we

have been able to bring patients out of an attack and allow them to lapse into one.

When given by mouth it appears in the blood chiefly as thiocyanate and can be measured by the usual method. Thus the acute intravenous effect which is due to the nitroprusside molecule is very different from the thiocyanate effect resulting from the conversion in the body of nitroprusside to thiocyanate.

Thus you will see that our philosophy of treatment is based on the belief that hypertension has multiple mechanisms; that control of the vascular disease is primary rather than control of arterial pressure alone; that until safer drugs are available early hypertension with imperceptibly advancing vascular disease should not be treated with the currently available drugs because they are not without danger; that each individual drug or diet should be demonstrated to be effective before other drugs are used; and finally that the treatment of hypertension is still very difficult, costly and time consuming.

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The Mechanism of Cardiac Failure*†

By LOUIS N. KATZ, M.D.

THE topic cardiac failure was chosen because my colleagues and I have been concerned with this problem for almost a quarter of a century. In this lecture I propose to outline my present concepts based on the evolution of thinking, which our work in this field and the impact of the literature has had upon it. I shall give scant attention to the work of others, not because their work is unimportant, but because time is limited and the material to be covered extensive.

WHAT IS CARDIAC FAILURE?

At the outset, let us define the task of the heart. It is the task of the heart to supply an adequate quantity of blood to meet the requirements of the various organs in the body at rest and during activity, so that they may perform their several functions without handicap. A heart that does this is competent. One that does not is incompetent. But an incompetent heart is not only one that fails to pump the proper amount of blood to the organs; it may be one which does pump an adequate amount of blood, but in doing so it requires adequate compensatory mechanisms. Therefore, incompetence of the heart includes two concepts. The first is that the heart fails to do its assigned task because the compensatory mechanisms are inadequate. The second one is that it does its assigned task because the compensatory mechanisms are adequate. Encroachment upon cardiac reserves occurs therefore whenever the heart becomes incompetent.

An incompetent heart with an inadequate output exhibits "forward failure" phenomena. An incompetent heart with an adequate output exhibits congestive phenomena behind the incompetent chamber. An incompetent heart with an inadequate output may show such congestive phenomena also, in addition to "forward failure."

Failure of the circulation in supplying the organ needs at rest or during effort may be cardiac or extracardiac. Extracardiac circulatory failure may be due to peripheral vascular collapse, when the systemic peripheral vessels dilate and blood is pooled within them instead of being returned to the heart. It also occurs in shock, which should be clearly defined as a progressive oligemia with hemoconcentration and compensatory systemic vasoconstriction. Here too the decreased venous return to the heart is the primary mechanism for the inadequate circulation. In both of these circumstances, the inadequate circulation is not initially due to an incompetent heart, but is due to circulatory disorders in the vascular system. Thrombosis in major veins, or other forms of venous obstruction, is another mechanism interfering with the venous return to the heart, leading to circulatory failure without the presence of an incompetent heart.

Cardiac circulatory failure, in which the inadequate blood flow is due to an incompetent heart, need not always be myocardial in origin. It may also be due to: 1) a dynamically significant valvular dysfunction, as in severe stenosis or free regurgitation; 2) a pericardial tamponade, a concretia cordis or a constrictive pericarditis; or 3) a tachycardia with its associated reduction in minute filling time.

The recent trend of semantics in which the terms congestive failure, low output failure and high output failure, have come into vogue, has led to some confusion to the uninitiated, and these terms should be dropped. Low output failure is a loosely used concept, including many things. Low output of the

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heart may ensue for a number of reasons and need not be primarily cardiac. When, however, in the course of shock or peripheral vascular collapse, or any other extracardiac mechanism leading to low output, incompetence of the heart ensues, then the latter can contribute to the low output.

High output failure is a misnomer that can only confuse the issue. High output of the heart is a compensatory mechanism which enables the body to get an adequate supply of oxygen for the tissues, when this is impossible at normal levels of output. This may ensue in arterial hypoxemia (e.g., anemia, inadequate ventilation in the lungs), in hyperthyroidism and in some avitaminoses. In some fashion the output of the heart per minute is augmented in these circumstances. If the strain is too much for the heart then it becomes incompetent and cardiac circulatory failure ensues even though the cardiac output may still be above the average normal. Chronic cor pulmonale is a frequent example of this circumstance.

Congestive failure too is a misnomer. Congestion may accompany incompetency of the heart whether or not there is cardiac circulatory failure. It may also ensue from disorders of the vascular system when the heart is competent. The mechanisms are in part vascular and in part renal; the latter are dealt with below. The former represent damming up behind the obstruction, whether this be a narrowed vein, a stenosed valve or an incompetent chamber of the heart, with the resulting consequences of this congestion. It may be behind the left or behind the right heart. Such congestion in the pulmonary veins impairs the ventilatory indices, increases the residual volume of the lungs, decreases the vital capacity and leads to pulmonary edema, first manifested by rales. It also leads to elevated "wedge" pressure and often to pulmonary arterial hypertension. Such congestion in the systemic veins leads to venous hypertension and engorgement, liver enlargement, anasarca and edema, as well as to interferences with the most effective operation of the various organs including the heart itself. Such states have been called "left" and "right heart failure."

Not only is the heart attuned to put out as much blood as it receives when in dynamic equilibrium, but this applies equally to each individual side of the heart. Thus, in dynamic equilibrium, the right and left ventricles pump out equal amounts of blood, whether this is low, high or average. Only when a patient is going into circulatory failure, coming out of it, or is moribund, is there any extended period of disequilibrium between the two hearts, as far as their minute output is concerned. So called "right" or "left heart failure," or more properly circulatory failure due to right or left heart incompetency, therefore, is not a disparity in output of the two sides of the heart. A moment's reflection will show that if the left heart were to pump 5 cc. more per stroke than the right, and if the right ventricle pumped 60 cc. per stroke and the heart beat 80 times per minute, and if the circulating blood volume is of the order of 5 liters, then in about 10 minutes all of the blood would have been pumped into the systemic circuit and none would remain in the lungs. This *reductio ad absurdum* is simply mentioned because of the loose thinking sometimes encountered in dealing with this subject.

One of the problems that has become of practical significance latterly, is the identification of how much of the lung congestion is due to mitral stenosis or mitral regurgitation and how much is due to a myocardial incompetent left ventricle. Furthermore, as every clinician appreciates, pulmonary disease itself produces signs, symptoms and changes in the laboratory measures of ventilatory efficacy in many respects imitative of that produced by an incompetent left heart.

It is thus apparent that heart failure arises from incompetency of the heart, sometimes leading to cardiac circulatory failure—an entity distinct from extracardiac circulatory failure—and sometimes leading to congestion. Furthermore, it should now be clear that not

all forms of incompetency of the heart are due to *myocardial* incompetency; they may result from abnormalities of other parts of the heart's structure or from disturbances in its rhythm. Finally, even the normal myocardium may be put to so much strain that its reserves are exhausted, and it too can become incompetent under these excessive conditions of stress. The distinction between a normal and a diseased myocardium is that the stress required to lead to this breaking point is less for the diseased than for the normal myocardium.

REGULATION OF THE NORMAL CARDIAC OUTPUT

The heart normally is so attuned that it pumps out, over any extended period of time, as much blood as it receives. In this respect, it is no different than the peripheral circulatory tree, which ordinarily forwards to the heart as much blood as it receives over any extended period of time. A number of servomechanisms are involved in this fine attunement of the circulation. Some of these are mechanical, some are humoral and some are neurogenic.

The most important of the humoral mechanisms are those involving the hormones of the adrenal medulla, l-epinephrine and l-norepinephrine, although doubtlessly other hormones, especially those of the adrenal cortex and pituitary, play their role. Closely bound up with the adrenal medullary hormones are the autonomic nerves which richly innervate the heart and peripheral blood vessels. They are linked with end organs, both chemo- and baroreceptors, located in the lungs, in the pulmonary and systemic vascular trees, and in the heart itself. The autonomic nerves are also influenced by messages relayed from end organs located in various somatic structures, including the special senses. They are also subject to the outpourings of the several stations in the central nervous system which constitute a complex cybernetic arrangement, far more complicated than that used by engineers.

A little more needs to be said about the mechanical factors controlling the flow of blood in the periphery. The capacity of the peripheral vascular bed is subject to change by humoral and neurogenic influences. This can occur by opening or closing of blood reservoirs and so adding or extracting blood to that in active circulation. In like manner, changes in venomotor tone may strikingly alter the capacity of the peripheral vascular bed, shifting blood to or away from these vessels, which constitute a large variable capacity. Similarly, vasomotion in the smallest vessels may be enhanced leading to accelerated forward flow. This acceleration of forward flow is brought about by virtue of the presence of valves in the circulatory tree which converts any intermittent forces operating upon the blood into forward flow. Such intermittent forces may also be caused by the movements of the innumerable villi in the intestines, by the partial tetanic contraction of the skeletal muscles which gives them their tone, by the motions of the limbs as in walking, and by the swaying accompanying the maintenance of an upright stance. Just as significant is respiration itself, since the thorax and abdomen can be considered as alternating bellows. Even the heart plays its role in this regard, over and above the *vis a tergo* it imparts, some of which still remains when the capillaries are reached. Thus, during its systole, the A-V junction moves toward the apex, tending to cause a drop on the pressure within the atria and thereby facilitating the flow of venous blood toward the heart.[1]

There are thus a number of factors which adjust venous return to the heart and act as a powerful adjuvant to the pumping power of the systole of the ventricles. To them must be attributed a major part in maintenance and regulation of blood flow.

Adjustment of the heart itself also plays an important role in regulating the cardiac

[1] This motion of the base of the heart toward the apex during systole has another pumping effect: the aorta and pulmonary artery are elongated while their valves are open, so that when these vessels shorten again in diastole with the valves closed, a small amount of blood is, as it were, "lifted" and added to that already ejected by the heart during its systole.

output. In part, this is brought about by variations in heart rate, dependent upon the action of the nerves supplying the heart, aided and abetted by the adrenal medullary hormones. In part, cardiac output is dependent upon the size of the ventricles when systole begins, that is, upon the right and left ventricular end diastolic volumes. This in turn is dependent upon the systolic residue—the blood not pumped out in the previous systole, the tone of the ventricles which determines its resistance to filling, and the duration of diastole, especially the period of its rapid inflow phase (*Fig. 1*). In addition to the action of end diastolic volume and heart rate, both of which are partly determined by extrinsic conditions lying outside the heart, there is another mechanism altering cardiac output which is dependent upon change in the contractile power of the heart. This last is affected by extrinsic influences, resulting chiefly from alterations in the tone of the cardiac nerves and in the hormonal content, especially of adrenal medullary hormones, present in the blood irrigating the heart.

In order for the heart to adjust its cardiac output, alterations in its energy releases take place. These, as ordinarily measured in terms of cardiac oxygen consumption, are determined not only by the end diastolic volume of the ventricles, but also by the character of the actual contraction of the ventricles and by extracardiac neurogenic and humoral mechanisms. When the work of the heart is measured in terms of the product of cardiac output the blood pressure in the aorta and pulmonary artery, and this is compared with the oxygen consumed by the heart to do this work, it is found that the ratio $\frac{\text{work}}{\text{oxygen consumed}}$ is quite variable at any end diastolic volume. In fact, oxygen consumption may go down as work increases even though heart size is augmented and heart rate unchanged. This demonstrates that cardiac oxygen consumption like cardiac output is determined by other factors in addition to end diastolic volume.

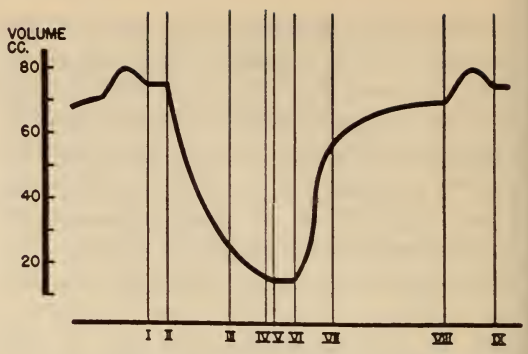

FIG. 1. Diagram of the volume curve of one ventricular cavity of the human heart at an assumed rate of 80 beats per minute, a stroke volume of 60 cc. and a systolic residue of 15 cc.—based on the studies of Wiggers and Katz (2). The curve starts in diastole. When the impulse in the sinus node spreads to the atria it causes them to contract and then relax (between VIII and IX and the homologous part of the curve ahead of I). The atria contribute little to filling; about 5 cc. net at ordinary heart rates. Actually while they add 10 cc. during their contraction they "take back" 5 cc. during their active relaxation. The impulse reaches the ventricles at I, and they begin to contract, at first isometrically (between I and II). Then ejection begins. In the short period of time, from II to IV, the blood is ejected from the ventricle (except for the systolic residue). Most of the blood is expelled during the rapid ejection period (II to III) and the remainder in the reduced ejection period (III to IV). Diastole begins at IV with a short protodiastole phase (IV to V) and an isometric relaxation period (V to VI). Most of the filling of the heart occurs in the rapid inflow phase (VI to VII). Filling here is just as brusque, and the period of filling is just as short, as that of the rapid ejection phase. In other words, the heart fills with a rush over a short period and not deliberately and uniformly over the whole of diastole. After rapid inflow, there is the period of passive filling, diastasis (VII to VIII), due to the *vis-a-tergo* of the blood coming back to the heart.

WHAT DISEASE OF THE HEART DOES

Let us now turn to disease of the heart and see what it does. Disease may increase the stress upon the heart. It may lead, for example, to systemic hypertension. It may lead to pulmonary arterial hypertension which has been demonstrated by catheterization to occur often, is a frequent complication of a strained left heart, and has as its clinical measure, crude though it be, accentuation of the second pulmonic sound. Disease may lead

to increased venous return because often the body metabolism is increased; metabolism is increased either because of the dyspnea produced, the restlessness of the patient, or an associated hyperthyroidism. Added to this, there is an increased venous return whenever anemia or hypoxemia complicates the picture, or when there is a chronic cor pulmonale. Certain vitamin deficiencies are another cause for increase in venous return in heart disease. In addition, disease may lead to valvular stenoses, valvular regurgitations, obstructions, atresias, coarctations, and shunts. These hidden stresses must be uncovered from their concealment by the examining physician.

The diseased heart will respond to these loads in the same way as the normal heart. It will call for a mobilization of compensatory mechanisms much as in the case of the normal heart. By so doing it will cut down the cardiac reserves.

Disease of the heart may decrease the upper limits of the adjusting compensatory mechanisms from which benefits may be derived and in this way also reduce the cardiac reserves. Thus, for example, the turning point from benefit to detriment as far as heart rate is concerned will occur earlier. This is demonstrated constantly by the relatively greater seriousness of paroxysmal tachycardia of equal degree in hearts that are diseased than in those that are not. In the case of hypertrophy, the presence of serious coronary disease leading to narrowing of the arteries will summate with the normal factor limiting hypertrophy, so that there will be less chance for maximal hypertrophy than in the normal heart. Heart weight is a deceptive measure of heart hypertrophy since it also weighs tissues in the heart other than muscle, viz., fibrosis and necrosis. Proper evaluation of true hypertrophy should take this into account. The upper limit of dilatation is also reached sooner in some forms of heart disease. It would seem that under certain circumstances the heart cannot dilate as much when it is diseased as normally before reaching the point where the dilatation is detrimental rather than beneficial. While too little is known about the detailed effect of disease upon the heart's contractile power, it is obvious that if the machinery of the heart is impaired, the effectiveness of extraneous mechanisms in increasing contractile power may be lowered. Thus, in these several ways disease of the heart by reducing the maxima of compensation from which benefits may be derived cuts down the reserves of the heart.

Finally, disease of the heart may impair the contractile power of the heart. When it leads to an obvious anatomical defect like myocardial infarction, which may destroy the machinery of up to one-fourth of the left ventricle or more, the defect in contractility is obvious and apparent. Disease may operate more subtly without such gross change. This may be revealed as cloudy swelling or fatty degeneration histologically, but often it is more subtle than this in lessening cardiac contraction and relaxation. We know so little about the details of the chemistry of this machine, that I will not indulge in any speculations on this topic. When heart disease alters the contractile machinery of the heart, the heart may work inadequately. The heart compensates for an impairment in contractility in the same manner as it does for an increase in stress. At the bedside therefore, the demonstration of compensatory mechanisms may indicate an increase in stress upon the heart or an impairment in its contractile power.

STRESS ON THE HEART AND THE MANNER OF MEETING IT

In order to understand better the subject of myocardial incompetence and the sequences resulting therefrom, I think we must turn to the normal heart and consider the stresses to which it is subjected and the compensatory mechanisms by which it meets these stresses. Stress upon the heart is threefold in character: It may be due: to an increase in the venous return, i.e., in its input load; to an increase in the blood pressure of the systemic or pulmonary arterial system, i.e., in its re-

sistance load; or to certain hidden loads not so easily revealed. Exercise and many emotional disturbances produce an increased input load. They also lead to an increased resistance load on the left heart and often also on the right. Trauma may produce some hidden loads in an otherwise normal heart. These increases in load have been reproduced in the experimental animal and the mechanisms by which they are met studied. What are these compensatory mechanisms? They are four in number:

1. There is dilatation.
2. If time elapses, there is hypertrophy.
3. There is tachycardia.
4. There is an increase in the contractile power of the myocardium produced by hormonal, humoral or reflexogenic mechanisms.

These same mechanisms, as already hinted, operate also upon the diseased heart when its load is increased or when its contractile power is impaired.

Dilatation is a simple mechanism resident in the heart and can be seen in the isolated heart, and so may be considered a primary mechanism which is able to attune the output of the heart to its input. At the bedside dilatation of the heart should be considered compensatory to enable the heart to meet an increased load. In this modern era of catheeterization, too many physicians imagine that the pressures in the heart at the end of diastole are a good measure of the size of the heart at that time. Actually the relationship between the end diastolic volume and the end diastolic pressure is not linear, but curvilinear (*Figs. 2, 3*). There is therefore under ordinary circumstances little or no change in the end diastolic pressure with rather large changes in end diastolic volume. It is to the end diastolic volume change that the ventricle's energy release, ability to work and pump blood, is related, and not necessarily to its end diastolic pressure. The difficulties of obtaining information regarding end diastolic volume should not permit loose employment of end diastolic pressure, or worse still, the

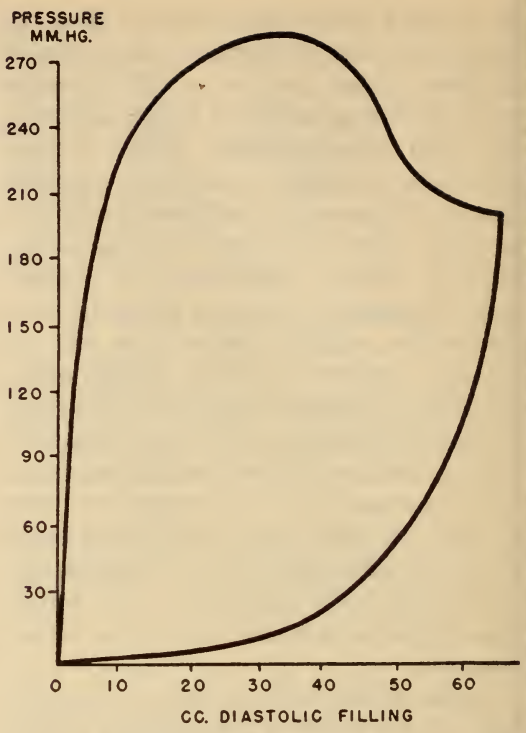

FIG. 2. A diagrammatic representation of the distensibility (P/V) curve of the fully-relaxed (lower) and fully-contracted (upper) left ventricle. It will be seen that at volumes between 0 and 20 cc. the change in pressure at the end of diastole is minimal. Only above 40 cc. does the pressure change become marked. On the other hand, the pressure change at the end of systole is marked at volumes between 0 and 10 cc., reaching a maximum at about 35 cc. and then declining. In isobaric contraction the change in volume during systole and diastole is set on a horizontal line at the level of pressure at which the heart contracts and relaxes, the limits being determined by the two P/V curves. In isovolumetric contraction the change in pressure during systole and diastole is set on a vertical line at the level of the diastolic filling at which the heart contracts and relaxes, the limit being determined by the two P/V curves. Under ordinary conditions of the heart beat, a closed figure is set up (a work-diagram) which begins and ends at the fully relaxed P/V curve, and is determined by the conditions under which the heart begins its systole. The shapes of the systolic and diastolic portions of the curve, and the point where the curve of the work-diagram intercepts the fully contracted P/V curve, are determined by the conditions under which its contraction and relaxation take place. (Copied from Patterson and Starling, J. Physiol., **48:** 465–513, 1914).

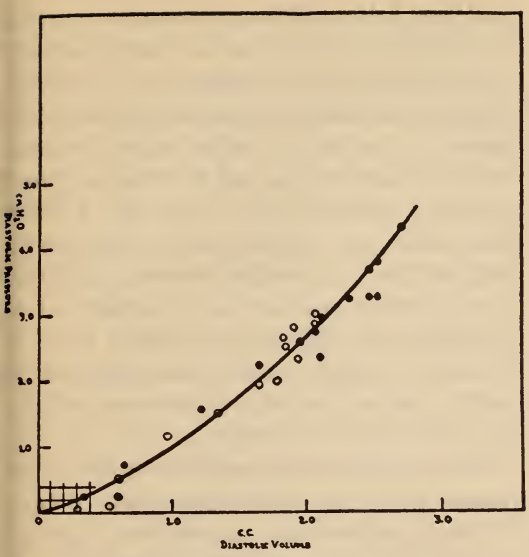

FIG. 3. Diagram of P/V ratios in the fully-relaxed ventricle of the turtle, when it is relaxing nearly isobarically (closed circles) and when it is relaxing isovolumetrically (open circles). Note that both sets of points lie along the smooth curved line (From (5)).

average or mean atrial pressure as an index of the adjustment of the heart by dilatation to an increased load—an error that has unfortunately crept into modern thinking, on the part of certain individuals.

Hypertrophy is another mechanism which, by increasing the mass of the heart, permits it to release more energy so that it can overcome the increased load. It requires time, however, and is not available at once but comes into play progressively if the load is sustained over time. We do not know the mechanism of cardiac hypertrophy, although we have reason to believe that it is associated with dilatation, with relative hypoxia and with relative increase in the work of the heart, and is, in some fashion, induced by the release of certain hormones of the pituitary gland. The mechanism of hypertrophy needs intensive exploration. Hypertrophy will occur in a normal heart subjected to increased load as well as in a diseased heart. Obviously therefore, both dilatation and hypertrophy are not necessarily signs of heart disease unless it is clear that they occurred without an increased load upon the heart.

Tachycardia which operates in the intact animal, and is not seen ordinarily in the isolated denervated heart, is a mechanism brought about in some fashion by an increased load. It would take us too far afield in this discussion to enter into the several mechanisms by which this tachycardia could be produced. Suffice it to say that it involves a lessening in tone of the cholinergic nervous mechanism and an enhancement in tone of the adrenergic nervous mechanisms, in all likelihood aided and abetted by the release of l-norepinephrine and l-epinephrine, with the possibility of other humoral agents also operating. Tachycardia, too, is to be considered a compensatory mechanism as easily available as is dilatation to permit the heart to overcome an increased load.

Closely allied to this are changes in the intrinsic machinery of the heart, part of which may operate upon the viscous-elastic properties which we call its tone, but more primarily they operate upon the machinery of its systole, its contractile power. Just like tachycardia, so these changes in the contractile power of the heart are brought about by reflexogenic and hormonal mechanisms, and it would have been surprising indeed if in the intact animal this had not developed. It is not too difficult to show upon the exhibition of sympathetic nerve stimulation or the administration of the mixed epinephrine, as I did as far back as 1918, that such changes can be produced in the contractile power of the heart without dilatation and independent of the tachycardia (*Fig. 4*). Exactly how this is brought about and upon which part of the intricate machinery of fat and carbohydrate metabolism—whether upon glycolysis, the Krebs cycle, the actin-myosin mechanism, or the ionic milieu surrounding the muscle—remains to be clearly established. The department is now engaged in a long-term evaluation of this problem. Suffice it to state that tachycardia and changes in contractile powers of

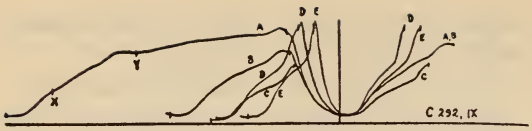

FIG. 4. A series of volume curves of the open-chested anesthetized dog drawn so as to superimpose the end of systole of the several beats, in order to show the effect of vagus stimulation (A and B) and epinephrine effect (D and E), as compared with the control (C). Attention is drawn primarily to the shorter duration and accelerated rate of ejection which was produced by epinephrine. These changes are disproportionate to the changes in heart rate and end diastolic volume, indicating a specific action of epinephrine upon the contractility of the heart (From (2)).

the heart, which are extracardiac in their mechanism, play as important a role as do the intrinsic adjustments of dilatation and hypertrophy.

When all four compensatory factors are simultaneously operative, they are interdependent; the more there is of one, the less need there is for the others to come into play. It would appear that dilatation is one that gives way, the one that is held more in reserve; so is tachycardia. Thus, for example, we are all aware of the fact that a patient with essential hypertension may for years have no tachycardia or no dilatation of his heart, the compensatory mechanism to meet the increased resistance load being accomplished by hypertrophy of the left ventricle.

CARDIAC RESERVE

One of the concepts that has been loosely employed is the term cardiac reserve. From our work and the impact of this work upon our thinking, I believe, cardiac reserve can be defined more precisely in terms of dilatation, hypertrophy, heart rate and contractile power, since for each of these there is an upper limit beyond which further increase is not possible or, if possible, becomes detrimental instead of beneficial. Cardiac reserve according to this concept is the difference between the size of the heart existing under the given load and the upper limit from which benefit can be derived, it is the difference between the heart weight existing under the load and that which can be produced, it is the difference between the heart rate existing under the load and the upper limit of heart rate from which benefits can be derived, and it is the difference between the contractile power of the heart existing under the load and the maximum that can be obtained. More properly, however, it is the sum of these four measures of cardiac reserve that gives an index of the total cardiac reserve available to meet increased loads. Now admittedly it is not always possible in our present state of knowledge to define clearly these measures of cardiac reserve, but this in no sense nullifies the merit of such a concept.

A few words are not amiss in regard to the reasons why there is an upper limit to each of these compensatory mechanisms. Thus, it has been established that the heart cannot dilate indefinitely and an increase in work be obtained. Actually, after a certain point, further dilatation leads to a decline in work (*Fig. 2*). An optimum thus exists in the size of a heart below which further dilatation is beneficial, above which it is detrimental. This fact has been established beyond question. It has been found to be true also when skeletal muscle is lengthened. I like to think in terms therefore of a dilated, compensated heart and an overdilated, failing heart.

The upper limit of hypertrophy is due to the fact that the number of capillaries do not increase as the heart hypertrophies. This inability of the capillaries to increase in number as the heart mass increases, puts an upper limit to the continued increase in heart weight. This is so since the oxygen and nutritive materials in the blood, and the carbon dioxide and waste products in the tissues move from one site to another by simple diffusion, dependent on their relative concentration at the two sites. As a consequence, the tissues further removed from the capillaries are less well serviced than those close to the capillaries, and as the distance from the capillaries increases, a point will be reached in which the material is not supplied or the waste not removed in adequate amounts commensurate with proper functioning. It is

on this basis that the maximum mass of the heart is limited.

When it comes to the extracardiac mechanisms leading to cardiac contractile power increase, the limits have not been thoroughly explored, but it is just a matter of logic to conceive that these stimuli cannot keep on continuously increasing the power of the heart. An upper limit must of necessity be reached. What it is, and how much greater than the ordinary contractile power of the heart it will be, remain to be clearly defined.

In the case of heart rate, a number of considerations come into play to point out that one cannot continuously increase the heart rate and get benefit therefrom. This depends in part upon the shape of the filling curve of the ventricles (*Fig. 1*) from which, if we ignore compensatory mechanisms as a first approach to our understanding, it will be seen that as the heart speeds up it affects at first only an abbreviation of diastasis, consequently the minute output will go up. This is so since stroke output depends on diastolic filling. When, however, the rate becomes so rapid that it cuts more and more into the rapid inflow phase, then the product of stroke volume and heart rate will decline. In fact, if the rate is so rapid that diastole consists only of isometric relaxation, then no filling will ensue and the heart will therefore have to draw upon its systolic residue for emptying, and this can soon be exhausted within a few beats. Thus, we have recorded pressure curves from the aorta in man in this department during premature systoles which occurred so early that no evidence of a pressure rise was seen. Compensatory mechanisms tend to overcome this mechanical obstacle of tachycardia, but even they cannot ultimately prevent this decrease in minute volume output with acceleration of the heart. That this is so is shown by the fact, as all of you know, that paroxysmal tachycardia can lead to circulatory failure, and/or to congestion—which can be remedied immediately upon the conversion of the tachycardia to the slower sinus rate.

Tachycardia also becomes detrimental because it cuts down the recovery time. The heart has very little ability to go into oxygen debt. It must make up in the next diastole or two for the oxygen that it goes into debt for during its systole, and since it is constantly beating, this cannot be out of balance for long without setting up a progressive deteriorating mechanism. Now, as the heart accelerates, the acceleration is primarily at the expense of diastole when recovery occurs, since systole varies only with the square root of the cycle length. Thus, progressive tachycardia puts an increasing strain upon the recovery mechanisms of the heart and a rate will ultimately be reached that will make the strain so great that the heart cannot by this mechanism meet the increased load.

Furthermore, with tachycardia it is clearly established that the mechanical efficiency, estimated in terms of oxygen consumed for work done, declines progressively more and more as the heart accelerates, and further, it is established without controversy that as the heart progressively speeds up, insufficiency of its coronary blood flow eventually ensues. Hence, not only is there strain upon the recovery time with acceleration because of less time to recover, but there is greater need for oxygen to do the work and there is less adequate coronary flow to permit this recovery to take place.

CONSEQUENCE OF INADEQUATE COMPENSATING MECHANISMS

Thus, it will be seen that the adjustments of the heart which compensate for an increasing load are limited in extent and when these limits are exceeded and when the reserves of the heart are exhausted, the heart cannot meet any further increase in load (*Fig. 5*). The classification of the American Heart Association could be viewed in these terms. With increasing load the upper limits for compensation are reached earlier in the class IV patient than in class III or class II (*Fig. 6*).

With progressive encroachment upon the cardiac reserves, a point will be reached when the compensatory mechanisms become in-

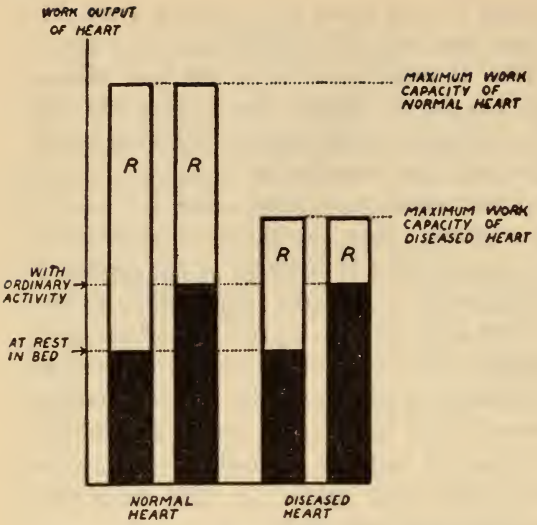

FIG. 5. Factors determining cardiac reserve (R) in the normal and diseased heart (From (15)). The reduction in R between bed rest and ordinary activity is shown both for the normal and for the diseased heart. Note, however, that the maximum capacity is reduced by disease. Cardiac reserve applies to all the compensatory mechanisms whether it be dilatation, hypertrophy, tachycardia or change in contractile power. Discussed in text.

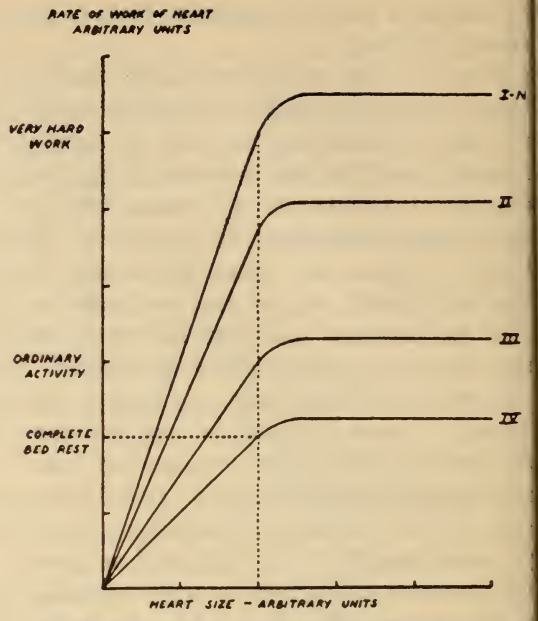

FIG. 6. Relation of work done to heart size in normal subjects (N) and patients with heart disease falling into classes, I, II, III, and IV of the American Heart Association Classification (From (15)). In Class I, the individual has the normal limitation in his ability to carry on activities. In the other classes, II with slight, III with moderate restriction of activity and IV requiring complete bed rest, the work done by the heart progressively declines at a given heart size. Therefore, to do the same amount of work as the patient in the class with less impairment of the heart, the patient requires a larger heart size. This encroaches on cardiac reserve. Discussed in text.

adequate. With inadequacy of the compensating mechanisms, whether brought on by increase in load, a decline in the maxima of compensatory mechanisms, or a decline in contractile power of the heart, a new chain of events will ensue. There will develop cardiac circulatory failure, at first only during periods of stress, but later also during ordinary activity and ultimately even at bed rest. Death will then not be far away.

Even before this, redistribution of the circulating blood volume will take place. Blood will be brought out of the reservoirs and the venules by neurogenic and humoral mechanisms in an attempt to bring about compensatory dilatation of the incompetent chamber of the heart. This blood together with the blood damming up behind the incompetent side of the heart leads to congestion and its sequelae (see above) and in some fashion also disturbs the excretory function of the kidney (see below). Thus, when the heart becomes incompetent, there is set up a complex chain of events involving many parts of the circulation and requiring the interplay of many humoral and neurogenic regulating mechanisms. Much remains to be learned concerning this phase of cardiac failure.

THE MECHANICAL EFFICIENCY OF THE INCOMPETENT HEART

I would like to turn now to the subject of the changes in the mechanical efficiency of the incompetent heart, a subject that has been rather forcefully debated in recent years. There are those who believe that heart incompetency is primarily the result of an impairment in the ability to employ for useful work the energy released. There are others, like myself, who believe that the primary defect

is in the release of energy and that the ability to employ this energy for work is not *primarily* impaired in *all* instances of heart incompetency. This is a fundamental and basic problem which may have to be reinterpreted as our knowledge of the intermediate metabolism of the heart grows and clarifies. I will not belabor you with many of the fascinating details of this controversy, but I would like to leave you with a few facts for orientation.

Mechanical efficiency, as an engineering term, is defined as the ratio

$$\frac{\text{work done}}{\text{energy required to do this work}}$$

calculated in similar units, e. g., joules, foot-pounds or large calories. The energy cost is ordinarily measured in terms of oxygen consumed, and it is assumed that the respiratory quotient is constant in the incompetent as compared to the competent heart, and this quotient may be assumed to be 1 or, as in the case of the average heart, 0.82. The term work has had many definitions, but it is more or less generally agreed that it should be defined as the useful work of the heart, that is, the amount of blood pumped by the heart multiplied by the mean blood pressure. The omission of kinetic energy in this calculation ordinarily introduces no serious quantitative error. In our calculations we have included the work of the right as well as the left heart, and have included the coronary flow in calculating the latter. Obviously by using this method of mean values in calculating the work, instead of integration formulae, certain other errors creep in but these are not ordinarily of sufficient moment to disturb the concept.

Using the simple method outlined above to calculate mechanical efficiency, it can be shown that mechanical efficiency can decline if tachycardia accompanies heart failure as is often the case (*Fig. 7*). But this is not primarily due to the heart failure, since tachycardia in a competent heart will have a like effect. Likewise it can be shown that if the cardiac output per minute declines as the heart fails, the mechanical efficiency will

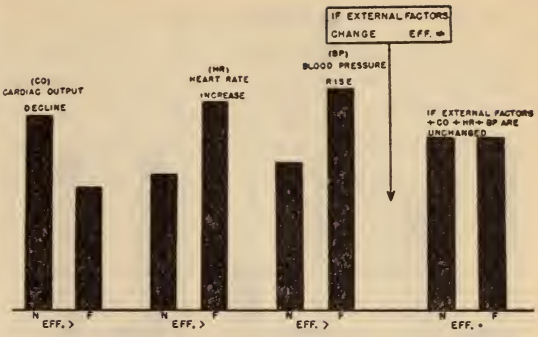

FIG. 7. The three sets of columns compare respectively, the cardiac output (CO), the heart rate (HR) and the systemic arterial blood pressure (BP) in cardiac circulatory failure (F) and normal (N). The change in each is such as to decrease mechanical efficiency (EFF) of the heart during failure. But like changes in these factors in the competent heart will have a similar effect on efficiency. A number of external factors which can change when the heart fails and thereby alter mechanical efficiency are represented in the square. Since their influence is not known, mechanical efficiency is marked as being changed ($\neq$). There is no reason to believe that similar effects would not be produced by such factors in the competent heart. In the last pair of columns is shown a situation actually obtained in the isolated heart (From (13)) in which the variables, external factors, cardiac output, heart rate and blood pressure were kept constant and the mechanical efficiency, consequently, remained unchanged. Discussed in text.

decline (*Fig. 7*), but this too is not primary with failure, since it will occur with low output even in the competent heart, as in cases of early shock. Furthermore, if an increase in the pulmonary or systemic arterial pressure, an increase in resistance load, occurs, this too may have a tendency to alter the mechanical efficiency in a downward direction (*Fig. 7*), but this again is not primarily heart failure, since a similar effect will occur under like circumstances in the competent heart. In our own experience, with isolated hearts whose work has been kept constant despite their progressive incompetence, we have found no change in the oxygen consumption of the heart even though the heart dilated in order to maintain this work.

How can we be sure that incompetence is of the same character in all circumstances? Actually, I believe it is not. It may develop

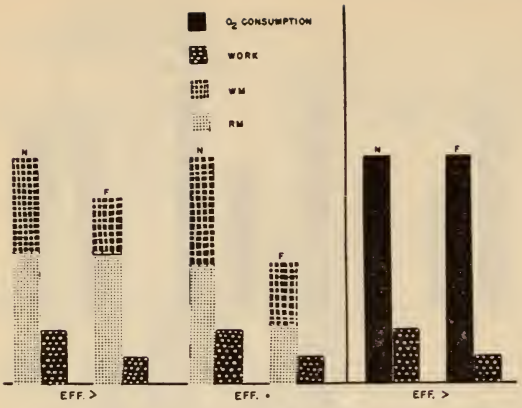

FIG. 8. A series of hypothetical circumstances which might be conceived to occur in failure of the heart. In the first set of columns on the left, a comparison is made of the oxygen consumption and work in the normal (N) and in the failing heart (F). The oxygen consumption is divided between that necessary to supply energy for work (WM) and that necessary to maintain the machinery in repair (RM). It is assumed that failure did not affect RM and that the ratio—work/WM was unchanged in that both declined proportionately. The consequence is that the mechanical efficiency (EFF.) declined. In the middle set of columns it is assumed that WM and RM decline proportionately as the work declines with failure of the heart. Under these circumstances, the mechanical efficiency does not change as the heart fails. In the set of columns on the right, conditions are compared between the normal and the failing heart, on the assumption that the oxygen consumption is unchanged despite a decline in work. This would lead to a decline in mechanical efficiency. This I believe does not occur. Discussed in text.

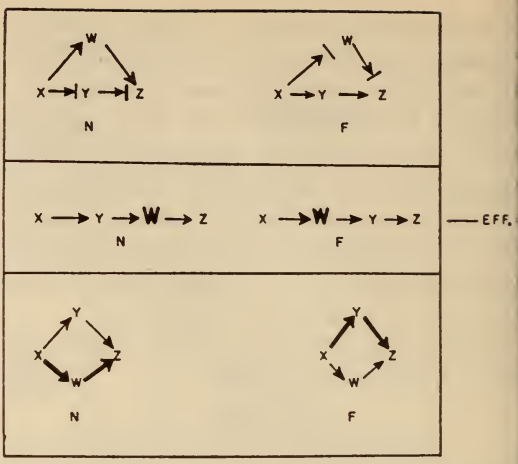

FIG. 9. This figure shows another group of possibilities which would alter the mechanical efficiency (EFF. ≠) when the failing heart (F) is compared with the normal (N). In the top row, it is assumed that the metabolic process changes from X–W–Z to X–Y–Z when the heart fails. In the middle row, it is assumed that failure alters the reaction sequence from X–Y–W–Z to X–W–Y–Z. In the lower row, it is assumed that the dominant path of chemical change alters when the heart fails as indicated by the change in thickness of the arrows. Discussed in text.

in one fashion under certain conditions and in another fashion in other circumstances. It is erroneous to assume that incompetence of the heart is identical under all conditions.

When we view the mechanical efficiency of the heart even under the best circumstances, we find that it really is at most of the order of 30%. Apparently the rest of the oxygen, or a large part of it, is used to keep the machinery in repair, i.e., to make up for the wear and tear of the machinery, and not directly for its work (*Fig. 8*). Hence, as the work of the heart declines, there may be a *pari passu* decline of the oxygen needed for the work, but the reparative processes may go on at the same level as before and so the total oxygen may not go down as much as the work did, and hence the efficiency will decline. The contrary will be the case when the work of the heart is increased. Here the proportion of energy needed for work will be increased and that necessary for the reparative processes will be less percentagewise. Furthermore, to pursue these theoretical concepts, there is no guarantee that the rate and sequence of the many intermediate reactions involved during the systole and diastole of the heart will be the same in the incompetent as in the competent heart, or that even the same reactions are employed (*Fig. 9*)—and these circumstances obviously can lead to changes in the mechanical efficiency which may vary from one type of incompetent heart to the next, depending upon how the machinery is deranged. Therefore, the mechanical efficiency of the incompetent heart changes in a very complex fashion, especially when cardiac circulatory failure supervenes, all the details of which are not yet clearly understood.

It, therefore, behooves the clinician in his every day activities to avoid the term cardiac efficiency and speak more of the efficacy of the heart, a term which need not be confused with the more precise definition to which engineers have assigned the concept of mechanical efficiency. I would predict that in the coming years we will have considerable clarification of this aspect of the mechanics of the incompetent heart in failure as newer knowledge of the intermediate metabolism of the heart advances.

EDEMA FORMATION

In the final portion of this lecture I would like to turn to a different aspect of heart failure, edema formation, in order to emphasize that the syndrome of heart failure is a derangement of function occurring in a complex and interlocking fashion, and extending beyond the heart and the vascular tree. While the heart is the initiating mechanism, a chain of alterations is set up which make the syndrome of heart failure much more than primary incompetence of the heart. This is not to say that one must concentrate on the secondary mechanisms and forget the primacy of the heart, but it shows that heart failure like other syndromes is complicated and not simple. This can best be illustrated I think by discussing the mechanisms of cardiac edema. This is a subject with which this department has been concerned for a considerable period of time.

The heart initiates the mechanism which causes retention of water and sodium chloride, but this retention is in reality due to a disturbance in the kidney regulation, whose task it is to see that water and sodium chloride neither accumulate nor are depleted from the body. How does this come about? Recently it has been attributed to cardiac circulatory failure ("forward failure"), at least that occurring during periods of stress. It has been emphasized that under these circumstances the sodium chloride and water excretion is dependent upon the glomerular filtration rate. Some years ago we put this to the test by producing pericarditis in the unanesthetized dog (*Fig. 10*). By the use of irritating cellophane, an extensive pericarditis ensued and this led chronically to edema, and this edema developed long before any change in resting cardiac output, blood pressure, renal blood flow, or glomerular filtration rate, but went *pari passu* with the elevation in venous pressure. It is difficult to believe, that this could be produced by a "forward failure" mechanism which reduces the glomerular filtration rate and the renal plasma flow, and so presents the tubules with less water and less sodium chloride to excrete.

What does a reduction in renal plasma flow and in glomerular filtration rate do? This was studied recently by using renal artery constriction (*Fig. 11*), recovery from temporary renal artery occlusion (*Fig. 12*) and recovery from inferior vena cava occlusion above the liver which led to a reversible shock-like syndrome (*Fig. 13*). In all instances the renal plasma flow and the glomerular filtration rate declined, yet the kidney recovered its ability to excrete sodium chloride and water before it overcame the constrictive or post-occlusive decline in blood flow and filtration rate. It is interesting and well known that the kidney has a protracted period of vasoconstriction following occlusion. The associated changes in renal salt-water exchanges are not due to irreversible damage to the tubules since histological examinations fail to reveal any such changes, and furthermore in animals allowed to survive, renal hemodynamics quickly returned to normal. All of these procedures were carried out on the unanesthetized trained dog and it has been the experience of this department that it is best to obtain these results in the unanesthetized animal.

It would follow from these observations that "forward failure," insofar as it reduces the flow through the kidney and its glomerular filtration rate, has no consistent influence on the excretion of sodium chloride or water. The body reacts to a sodium chloride load with a sodium chloride excretory response

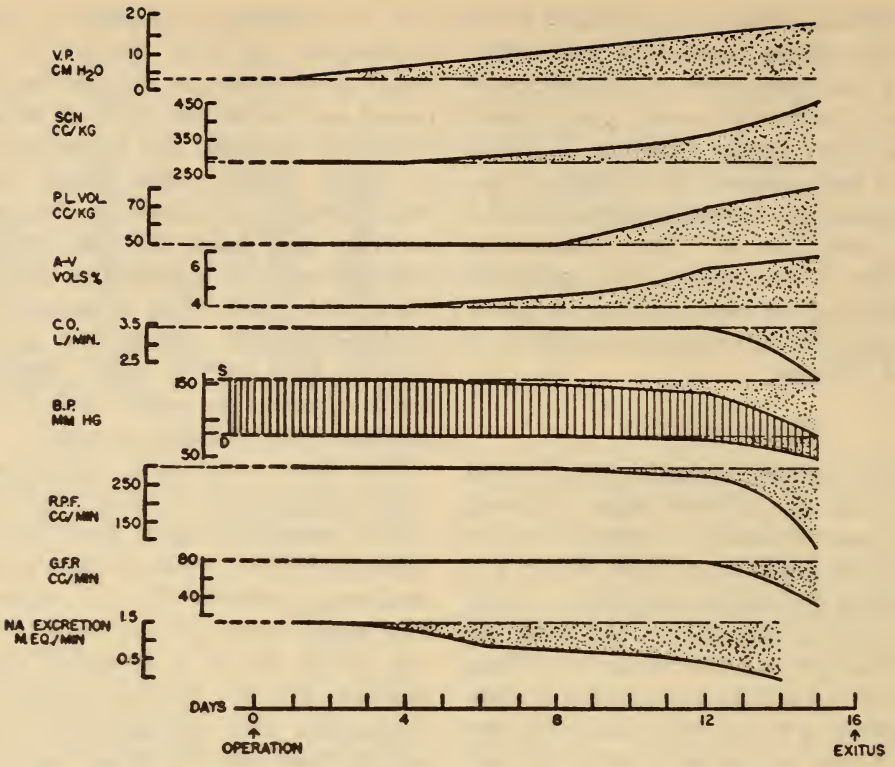

FIG. 10. Sequence of physiological changes in chronic experimental pericarditis with effusion: semi-diagrammatic summary of data obtained on nine dogs (25). V. P., peripheral venous pressure; SCN, thiocyanate space; PL. VOL., plasma volume; A-V, arteriovenous oxygen difference in volumes per cent of O_2; C.O., cardiac output; B. P., blood pressure (S, systolic and D, diastolic); R.P.F., renal plasma flow; G.F.R., glomerular filtration rate, Na excretion, sodium excretory rate in milliequivalents of sodium per minute, in response to an intravenous hypertonic saline load; (↑ Operation) day of operative placement of irritative cellophane bag about the heart, between visceral and parietal pericardial layers. Abscissa represents days postoperative to death (↑ Exitus). Discussed in text.

despite marked changes in the glomerular filtration rate and renal plasma flow. Yet in heart failure the body reacts as if the animal were sodium depleted (*Fig. 14*), despite the fact that actually the animal is overloaded with sodium chloride and with water. Why?

In order to answer this question we have carried out a series of experiments on acute and chronic vein occlusions. For example, when the inferior vena cava is partially occluded above the liver, the animal quickly develops ascites and this edema is sustained chronically. Associated with this there is sodium chloride and water retention (*Fig. 15*). In contrast, when the inferior vena cava is constricted above the kidney, either acutely or chronically, no edema develops. In the acute experiments there is only a transient effect in the sense of water and sodium chloride retention (*Fig. 16*). In the chronic experiments, no effect is observed (*Fig. 17*). This leads to the conclusion that while transitory elevations of renal venous pressure can produce temporary declines in renal plasma flow and glomerular filtration rate, and associated retention of sodium chloride and water, this quickly disappears and is not seen in animals with chronic renal venous pressure rise, provided no edema ensues. Consequently, one can say that decreased renal sodium chloride and water excretion (with normal renal blood flow and glomerular filtration rate) occurring

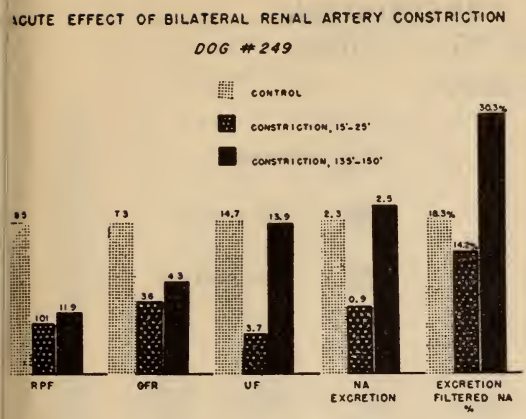

FIG. 11. Acute effect of bilateral renal artery constriction (37). RPF, renal plasma flow cc./min; GFR, glomerular filtration rate, cc./min; UF, urine flow, cc/min; Na excretion, meq/min. The numbers above the bars represent the numerical values in appropriate units.

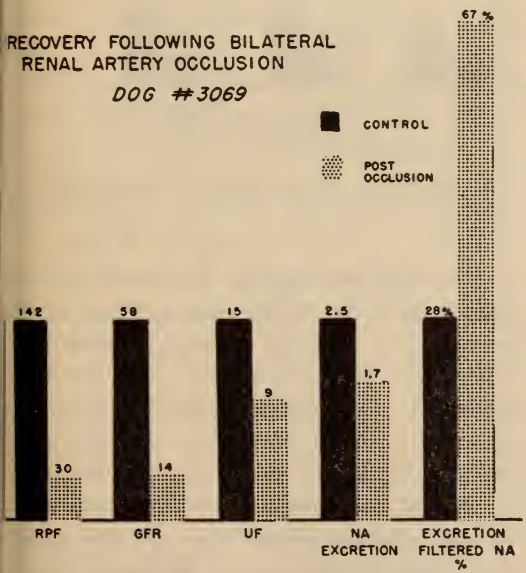

FIG. 12. Recovery following bilateral renal artery occlusion (35). Symbols as in *Fig. 11.*

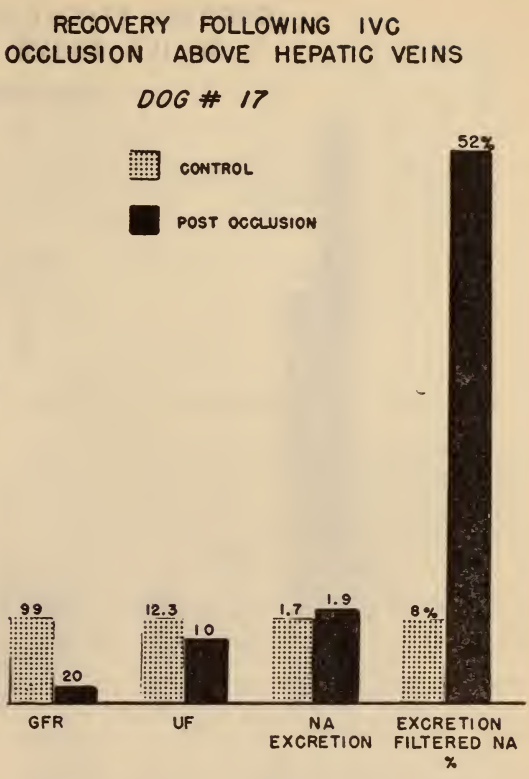

FIG. 13. Recovery following inferior vena cava occlusion above hepatic veins (35). Symbols as in *Fig. 11.*

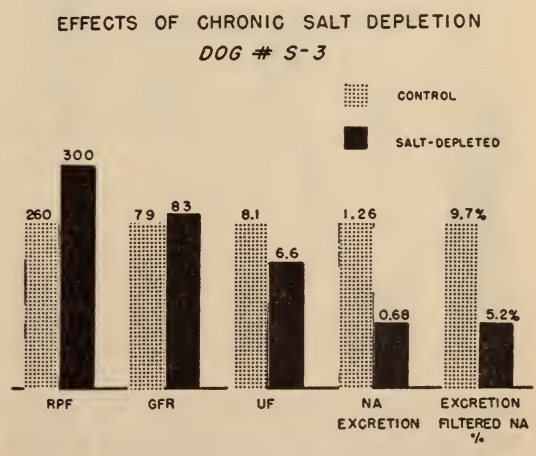

FIG. 14. Effects of chronic salt depletion (29). Symbols as in *Fig. 11.*

in association with the chronic ascites of inferior vena cava narrowing above the liver is not due to the elevated *renal* venous pressure which persists. On the other hand, inferior vena cava occlusion below the kidney does not lead to edema or to any change in water and sodium chloride excretion acutely or chronically, unless the femoral vein and epigastric vein are also occluded. Under these latter circumstances, edema will develop and sodium chloride and water retention will ensue (*Fig. 18*). It is obvious from such experiments

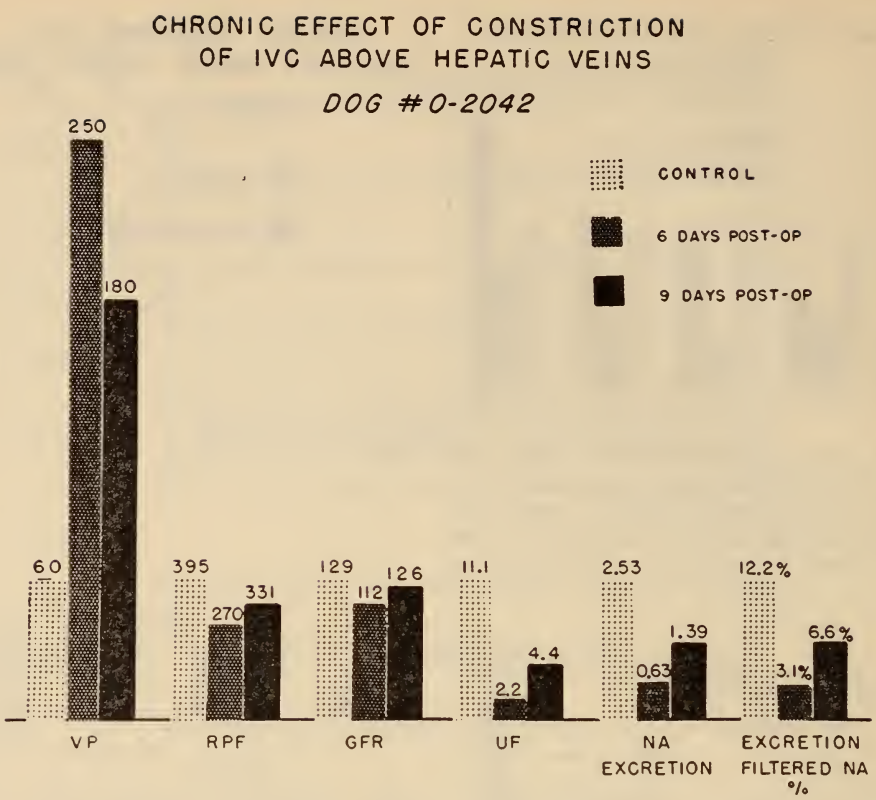

FIG. 15. Chronic effect of constriction of inferior vena cava above hepatic veins (27). VP, venous pressure, mm H_2O. Other symbols as in *Fig. 11.*

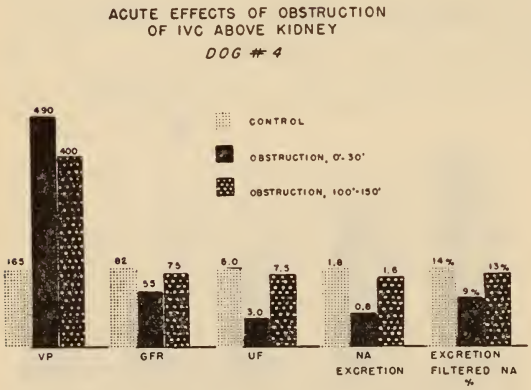

FIG. 16. Acute effects of obstruction of inferior vena cava above kidney (36). VP, venous pressure, mm H_2O. Other symbols as in *Fig. 11.*

that it is not necessary to interfere with the circulation of the kidney, of the adrenals, or of the liver to produce edema, and, more particularly, to disturb the excretion of sodium chloride and water by the kidney.

The possibility exists, of course, as has been claimed by others, that occlusion of the vena cava to the head, the superior vena cava, may have different effects. This we have tested. In acute experiments following such a procedure, neither edema nor any change in sodium chloride or water excretion occurred. In chronic experiments we have seen some animals develop edema (*Fig. 19*) and others not. Those animals which developed edema behind the region of occlusion showed sodium chloride and water retention in the kidney. Those that did not, showed no such effect. These experiments on the superior vena cava failed to reveal any evidence of any special volume receptors in the head—i.e., of receptors that would signal increased renal salt-water excretion as a result of cranial congestion. They failed to reveal that interference with the flow of blood to the hypothalamic and pituitary region has any extraordinary in-

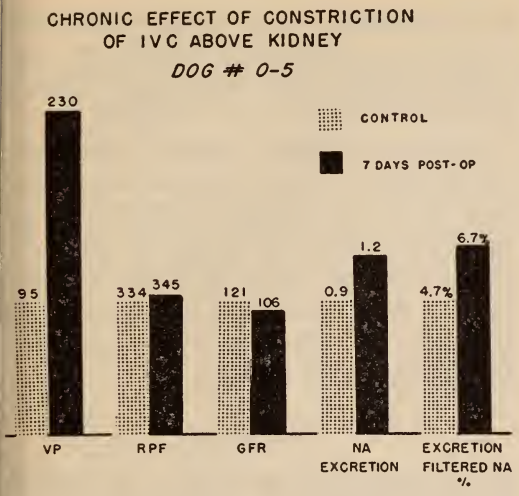

FIG. 17. Chronic effect of constriction of inferior vena cava above kidney (26). VP, venous pressure, mm H_2O. Other symbols as in *Fig. 11.*

fluence on sodium chloride and water excretion.

Finally, in some recent experiments in which mercurials were exhibited and found to inhibit sodium chloride absorption by the tubules, and in which sodium nitrate was substituted in part for the sodium chloride, the results suggested strongly that the mercurials operate primarily by interfering with the excretion of the chloride by the tubules, and that the changes in sodium, and presumably in water excretion, are secondary.

In reviewing our work on edema formation in congestion, we have come to the following conclusions: It is not stasis in any special area like the head, the kidney, the liver or the endocrines *per se* which causes sodium chloride and water dysfunction of the kidney, but it is stasis *per se*, since stasis even in a region not involving such organs can lead to a similar disturbance. It is not clear from our work, or that in the literature, whether it is the local venous hypervolemia, or the elevated venous pressure, or the transudation, or the local changes in the tissues, or the tendency toward hypovolemia in the rest of the circulation when part of the blood is so to speak impounded, which is the trigger mechanism. However, the disturbance associated with

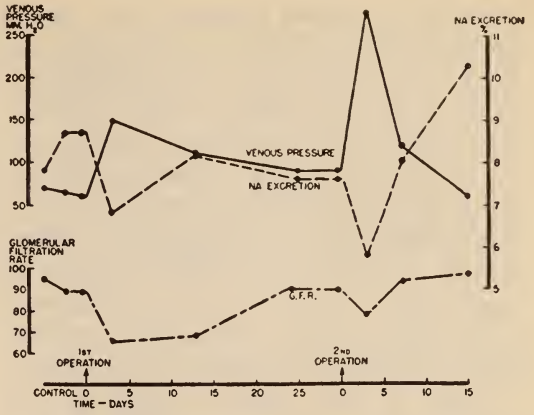

FIG. 18. Effect of elevated venous pressure in lower extremities on per cent Na excretion and GFR (28). First operation was ligation of inferior vena cava below the renal veins; second operation was ligation of femoral and inferior epigastric veins.

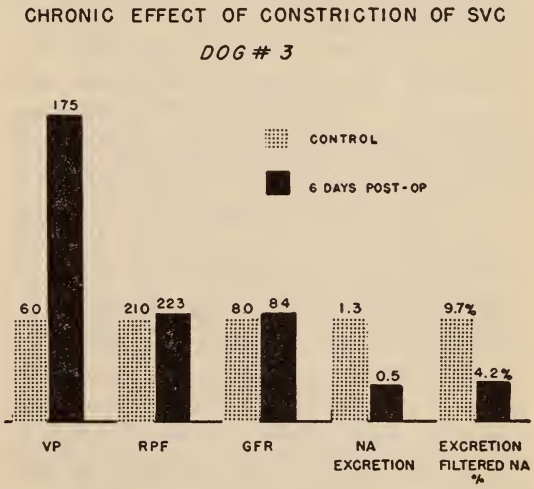

FIG. 19. Chronic effect of constriction of superior vena cava (28). VP, venous pressure, mm H_2O. Other symbols as in *Fig. 11.*

venous pressure rise in some fashion and independent of any special area, sets up a receptor-effector mechanism that adjusts the kidney excretion of sodium chloride and water so that they are retained. This can readily be brought out when the body is loaded with a sodium chloride solution. We used 1.5% sodium chloride or Ringer's solution at the rate of 6–10 cc. per minute. We do not know the location of the receptor, nor its character. We do not know whether hormonal factors are

involved, nor do we understand the role of the central nervous system in this mechanism. Work is now being pursued in this department to try to get the answers to these questions. It is apparent from our work, however, that the mechanism of sodium chloride and water disturbance operates in the tubules. It would appear that it is the reabsorption of sodium chloride and water that is affected, but it is possible that it may be in part an interference with actual secretion of sodium chloride and/or water from the blood into the tubules.

Edema in heart failure is caused by the heart, but the mechanism as outlined above involves a derangement of kidney function in which the kidney operates as if the body were depleted of sodium chloride and water despite the excess presence of both. In acute incompetence of the heart, the edema may be due in part to local transudation of fluid on a mechanical or reflexogenic basis, aided and abetted by "forward failure" which alters renal blood flow and glomerular filtration rate, and by "backward failure" which, by elevation of renal venous pressure, has the same effect. This reduction in glomerular filtration rate may operate to interfere with the renal ability to excrete sodium chloride and water (glomerulo-tubular imbalance). However, the renal mechanism so set up is quickly adjusted to and in chronic failure is of little importance. Similarly, during periods of stress there is in the cardiac patient a greater decline in renal flow and in glomerular filtration rate, due to the development or exaggeration of "forward failure" or of renal venous congestion (leading to further glomerulo-tubular imbalances). This effect upon the kidney during periods of stress is only part of the picture because such stress leads to widespread venous congestion in other areas. If general venous congestion is in some fashion responsible for the derangement of tubular salt-water excretion during the resting state, then this effect would be exaggerated during periods of bodily stress.

In summary, we believe that heart failure sets up a receptor-effector system that results in a disturbance in the ability of the renal tubules to excrete sodium chloride and water so that edema ensues. This in some fashion is associated with the venous congestion.

Analyses of similar complex interlocking disturbances in body function other than those of water and sodium chloride exchanges would be of benefit in completing our understanding of the entire syndrome of heart failure. They would help to improve the knowledge by which rational management and therapy can be planned.

CONCLUSION

In conclusion, you can see that the problem of cardiac failure is not a simple one as at first sight it might appear to be, and that its complexity is only now beginning to be appreciated. I predict that in the future our understanding will bring light upon the obscure relationships. At any rate you will admit that the functional viewpoints expressed concerning cardiac failure point to the direction from which illumination will come.

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Transactions of the Sections

SECTION ON GENERAL MEDICINE

25 January 1954

Relief of Parkinsonian Tremor and Rigidity by Ansotomy. Ernest A. Spiegel, M.D., and Henry T. Wycis*, M.D. (Discusser: Abraham M. Ornsteen, M.D.)

A New Compound for Intravenous Cholangiography—Biligrafin. David M. Sklaroff*, M.D., J. Gersohn-Cohen, M.D., Edwin M. Cohn*, M.D., and Theodore L. Orloff*, M.D. (Discusser: J. Edward Berk, M.D.)

Experiences with Combination Drug Therapy in Arterial Hypertension. David J. Reinhardt,* M.D. (Discusser: Joseph H. Hafkenschiel, M.D.)

One-year Follow-up of a Case with Thyroid Transplant. Julian A. Sterling, M.D., and Ralph Goldsmith, M.D. (Discusser: Edward Rose, M.D.) (*Abstract 1, below*)

22 February 1954

Sickle Cell Anemia in the White Race—*Report of Case.* Theodore H. Mendell, M.D., and Harold A. Wurzel*, M.D. (Discusser: Thomas Fitz-Hugh, Jr., M.D.)

Abnormalities in Esophageal Transport Associated with Dysphagia. Stanley H. Lorber, M.D., and Harry Shay, M.D. (Discusser: Walter H. Maloney*, M.D.) (*Abstract 2, below*)

Skeletal Manifestations of Sarcoidosis. George N. Stein*, M.D., Harold L. Israel, M.D., and Maurice Sones, M.D. (Discusser: Herman W. Ostrum*, M.D.)

Visualization of Intracardiac Calcification by Planigraphy. Jacob Zatuchni*, M.D., Louis A. Soloff, M.D., and Herbert Fisher*, M.D. (Discusser: Paul S. Friedman M.D.)

22 March 1954

Prevention of Gangrene by a Protective Coating on the Ischemic Foot. Meyer Naide, M.D. (Discusser: Theodore H. Mendell, M.D.)

Possible Use of a Phosphatase Cholesterol Index in the Differential Diagnosis of Cholangiolitic Hepatitis and Extrahepatic Biliary Obstruction. Harry Shay, M.D., Samuel L. Cresson*, M.D., and Herman Siplet*, M.D. (Discusser: Charles M. Thompson, M.D.)

Radioactive Colloidal Gold for Acquired Hemolytic Anemia Refractory to Splenectomy. George Wang*, M.D., H. S. Bowman*, M.D., and L. M. Tocantins, M.D. (Discusser: Lawrence H. Beizer, M.D.) (*Abstract 3, below*)

Nickel Poisoning: Clinical and Autopsy Studies on a Group of 100 Men Exposed to the Vapors of Nickel Carbonyl. F. William Sunderman, M.D., and John F. Kincaid*, Ph.D. (Discusser: Andrew J. Donnelly, M.D.) (*Abstract 4, below*)

26 April 1954

Jaundice Associated with the Administration of Chlorpromizine (Thorazine). Joseph M. Gambescia*, M.D., N. William Winkelman, Jr.*, M.D., Joseph E. Imbriglia, M.D., and Peter Galamaga*, M.D. (Discusser: John R. Neefe, M.D.)

Further Observations on Patients with Severe Hypertension Subjected to Adrenal Resection and Sympathectomy. William A. Jeffers, M.D., Harold A. Zintel, M.D., A. Gorman Hills*, M.D., Joseph H. Hafkenschiel, M.D., Stephen B. Langfeld*, M.D., Alfred M. Sellers*, M.D., and Charles C. Wolferth, M.D. (Discusser: Richard A. Kern, M.D.) (*Abstract 5, below*)

Histamine Gastric Analysis as a Screening Method in Gastric Cancer Detection: Preliminary Report. C. Wilmer Wirts, M.D. (Discusser: Paul C. Swenson, M.D.)

The Clinical Significance of the QS and

* *By invitation.*

QRS Deflection in the Precordial Leads of the Electrocardiogram, with Particular Reference to the Leads V_3 and V_4. Borys Surawics*, M.D., Robert Van Horne*, M.D., John R. Urbach*, M.D., and Samuel Bellett, M.D. (Discusser: Thomas M. Durant, M.D.)

SECTION ON MEDICAL HISTORY

28 January 1954

Sumerian Medicine: A Clay Tablet Inscribed with the Oldest Medical Inscriptions in Man's Recorded History. Samuel Noah Kramer*, Ph.D.

Physicians and Politics in the Revolution: The Case of Adam Kuhn, with a Note on Philip Turpin[1]. Whitfield J. Bell, Jr.*, Ph.D.

Dr. Joseph Bell, Dr. A. Conan Doyle, and Sherlock Holmes. Joseph V. Klauder, M.D.

25 February 1954

S. Weir Mitchell, Neurologist. Robert A. Groff, M.D.

Review of Letters Received by T. S. Kirkbride, 1840–1883, with Special Reference to Autographed letters of Psychiatrists. Clifford B. Farr, M.D., and Gertrude Stout*.

George de Benneville, Sr., and Early Colonial Medical Practices. Douglas Macfarlan, M.D.

25 March 1954

Medical Education and Practice in the Ohio Valley, 1780–1860. David A. Tucker, Jr.*, M.D. (Kate Hurd Mead Class of 1888 Lecture in Medical History, Woman's Medical College of Pennsylvania)

SECTION ON OPHTHALMOLOGY[2]

21 January 1954

Human Electroretinography in Physiology and Clinical Practice. Hermann M. Burian*, M.D.

18 February 1954

Ophthalmoplegias of Peripheral Origin. C. Wilbur Rucker*, M.D.

18 March 1954

Kronline Orbitotomy for Meningioma of Sheath of Optic Nerve (motion picture). Edmund B. Spaeth, M.D.

Experiences with Carbonic Anhydrase Inhibitors in Glaucoma. Irving H. Leopold, M.D., I. Jacob Eisenberg, M.D., and J. Yasuna*, M.D.

Radioactive Phosphorus in the Diagnosis of Intraocular Tumors. John Erbaugh*, M.D. (Discusser: Arno E. Town, M.D.)

15 April 1954

Congenital Corneal and Facial Anesthesia—*Case Report.* William C. Frayer*, M.D. (Discusser: George D. Gammon, M.D.)

Retinopathy in Five Hundred Unselected Diabetics—*Clinical Report.* Thomas H. Cowan, M.D., Paul Carmichael*, M.D., and Frank Campagna*, M.D. (Discusser: Stanley I. Spoont*, M.D.)

Nuclear Vertical Muscle Paralyses.—*Research Paper.* Fred Harbert*, Capt., MC, USN. (Discusser: Francis H. Adler, M.D.)

SECTION ON OTOLARYNGOLOGY[3]

20 January 1954

Osteoma of the External Auditory Canal. Oram R. Kline, M.D., and Rowan C. Pearce, Jr.*, M.D.

Prosthesis for Hearing. Robert J. Hunter, M.D.

Lethal Granuloma of Midline Facial Tissues. Arthur J. Wagers, M.D., Robert L. Breckenridge, M.D., and William H. Baltzell*, M.D.

Fenestration Operation—Long-term Results. Edward H. Campbell, M.D.

[1] Printed in the *Transactions & Studies*, 4th ser., vol. 22, no. 1, June, 1954.

[2] Abstracts of the presentations at this Section customarily appear in the *American Journal of Ophthalmology* and the *A.M.A. Archives of Ophthalmology.*

[3] Abstracts of the presentations at this Section customarily appear in the *A.M.A. Archives of Otolaryngology.*

17 February 1954

Otolaryngological Mishaps—A Confessional. C. Stewart Nash*, M.D.

17 March 1954[4]

Borderline Malignant Lesions of the Larynx. F. Johnson Putney, M.D. (Discusser: John F. Daly, M.D.)

Basal Cell Carcinoma of the External Ear—*Report of a Case with Recovery.* Herbert P. Harkins, M.D. (Discusser: Harry Rosenwasser, M.D.)

Newer Concepts of the Physiology of Waldeyer's Ring. Harry P. Schenck, M.D. (Discusser: Franz Altmann, M.D.)

[4] Joint meeting with the Section on Otolaryngology of the New York Academy of Medicine. Discussers represent the New York Section.

21 April 1954

Ossifying Fibroma of the Ethmoid Labyrinth—*Case Report.* Kelvin A. Kasper, M.D., and Enrique A. Vincens*, M.D.

Tuberculosis of the Larynx. William A. Lell, M.D.

Sundry Features of Otosclerosis. Maurice Saltzman, M.D. (Discusser: Matthew A. Ersner, M.D.)

SECTION ON PUBLIC HEALTH, PREVENTIVE AND INDUSTRIAL MEDICINE

25 March 1954

The New Education Program at Western Reserve. John L. Caughey, Jr.*, M.D. (Discussers: Curriculum Committee, John McK. Mitchell, M.D.; Pre-clinical Teacher, J. Earl Thomas, M.D.; Clinical Teacher, W. Edward Chamberlain, M.D.; Student, Ann Holsinger*.)

Abstracts

Abstract 1

One-year Follow-up of a Case with Thyroid Transplant. Julian A. Sterling, M.D., and Ralph Goldsmith, M.D.

A case is reported of a twenty-eight year old woman who had suffered tetany and hypothyroidism for more than ten years following total thyroidectomy.

This tetany was relieved by transplantation of parathyroid gland of homologous origin, using vascular anastomoses between the donor thyroid gland and the host. More than one year had elapsed since transplantation.

Coincidentally, evidence presented indicated that the patient's thyroid functions had returned to normal.

Donor gland has been obtained from an infant of 25 days.

Abstract 2

Abnormalities in Esophageal Transport Associated with Dysphagia. Stanley H. Lorber, M.D., and Harry Shay, M.D.

Roentgen studies of esophageal transport were obtained in 38 patients whose chief complaint was dysphagia and in whom no organic obstruction of the esophagus existed. With the patient sitting, 15 cc. of a barium-water mixture were administered orally and esophageal emptying was carefully timed. If emptying was incomplete in 3 minutes, esophageal retention was estimated. Similar observations were made after the consecutive subcutaneous administration of 5 mg. of Urecholine and 30 mg. of Dibuline, each study being performed at the height of drug activity. Each part of the study was repeated three times and, in addition, other drugs were investigated.

From the results of parasympathetic stimulation or depression one can divide these patients into 2 groups.

A. In 16 patients, diagnosed as having chronic cardiospasm, administration of Urecholine produced severe spasm of the lower esophagus similar to that induced by Mecholyl. Vomiting and substernal discomfort occurred in most. Administration of the parasympathetic depressant Dibuline not only relieved the Urecholine induced spasm but was followed,

in most, by an increase in esophageal transport over that of the control period. Nitroglycerin (0.4 mg.) administered sublingually was the most effective drug in producing esophageal evacuation.

B. In the remaining 22 patients, esophageal transport remained the same (6) or improved (16) after Urecholine administration but decreased after the administration of Dibuline. Patients in this group had the following diagnoses: Congenitally shortened esophagus with hiatal hernia, constriction ring of esophagus, esophagitis and normal esophagus.

The physiologic, diagnostic and therapeutic implications of these observations were stressed.

Abstract 3

RADIOACTIVE COLLOIDAL GOLD FOR ACQUIRED HEMOLYTIC ANEMIA REFRACTORY TO SPLENECTOMY. George Wang, M.D., H. S. Bowman, M.D., and L. M. Tocantins, M.D.

Four patients with acquired hemolytic anemia treated with either radioactive colloidal gold alone or radioactive gold in combination with ACTH and Cortisone are reported. Splenectomy was performed in all patients before the radioactive gold therapy but failed to have any effect on the hemolytic process. In three of the patients the hemolytic anemia was associated with chronic lymphocytic leukemia or Hodgkin's Disease. The other was "idiopathic." All had a positive Coombs Test.

Doses of 8 to 50 millicuries intravenously were used. All patients received one or more administrations of radioactive gold. Two patients received ACTH, and one patient received ACTH and Cortisone in addition to radioactive gold. All displayed complete clinical and hematological improvement. However, no substantial response was noted until radioactive gold was added to the therapeutic regimen. Improvement first became manifest 2–3 months after the drug was administered. Relapses in the hemolytic process occurred in three patients at various intervals after the initial radioactive gold therapy but were brought under control by subsequent administrations of the drug. One patient had a remission lasting two years. She then relapsed and was treated with the gold alone. A remission followed that has lasted four years. The Coombs Test remained positive throughout the course.

In acquired hemolytic anemia alteration of red cells by autoantibodies may invoke excessive erythrophagocytosis which further enhances blood destruction. Splenectomy removes an important but not all of the source of erythrophagocytosis. Radioactive gold is taken up by the reticuloendothelial tissue, notably the liver, and may eradicate a great portion of the remaining erythrophagocytic activity. The results indicate that the drug is particularly effective in the treatment of acquired hemolytic anemia that is refractory to both splenectomy and the corticosteroids.

Abstract 4

NICKEL POISONING: CLINICAL AND AUTOPSY STUDIES ON A GROUP OF 100 MEN EXPOSED TO THE VAPORS OF NICKEL CARBONYL. F. William Sunderman, M.D., and John F. Kincaid, Ph.D.

Clinical observations are reported on a group of individuals accidentally exposed to the vapors of nickel carbonyl. Of this group two died and many of the others were critically ill.

The symptomatology, course, and pathologic changes following acute exposure have been discussed.

The concentrations of nickel in urine were determined in samples obtained from exposed individuals. Our studies indicate that the nickel concentration in urine is increased many fold above normal after exposure. The concentration of nickel in urine appears to be correlated with the severity of exposure.

Mercaprol therapy was administered to 32 exposed individuals, 31 of whom survived. In so far as we are aware this is the first report of the use of mercaprol in the treatment of nickel carbonyl poisoning. The administration of mercaprol appeared to be beneficial in most cases. Its administration was attended by an increased excretion of nickel in urine and a

marked decrease in the concentration of nickel in blood.

Abstract 5

FURTHER OBSERVATIONS ON PATIENTS WITH SEVERE HYPERTENSION SUBJECTED TO ADRENAL RESECTION AND SYMPATHECTOMY. William A. Jeffers, M.D. Harold A. Zintel, M.D., A. Gorman Hills, M.D., Joseph H. Hafkenschiel, M.D., Stephen B. Langfeld, M.D., Alfred M. Sellers, M.D., and Charles C. Wolferth, M.D.

This report concerns the clinical course of 125 severely hypertensive patients subjected to adrenal resection and sympathectomy. Especial attention is directed toward 96 patients operated upon with an Adson type sympathectomy and either total or subtotal adrenalectomy. During a maximum of 4 years' observation 23% of the 125 patients have died, the cause of death in more than half of these being a stroke. Evidence is presented for continuing to follow the indications and contraindications for operation as previously chosen. Marked impairment of renal function is the most definite contraindication.

Blood pressure responses to operation among the 96 survivors are adjudged to be as follows: excellent 44%, fair 24%, poor 12%, failure 7%. Improvement has occurred with respect to the electrocardiogram (37%), heart size (34%), and ocular fundi (46%). Among the 96 survivors relief of congestive heart failure has been observed in 100%, of angina pectoris (71%), and of headache (70%). As measured by PSP tests and blood urea nitrogen, progressive impairment of renal function may occur occasionally, without regard to the postoperative blood pressure response.

Of 57 patients having a subtotal adrenalectomy, 15 now require no adrenal cortical replacement therapy. The course of these 15 patients does not suggest that regeneration of the remaining adrenal fragment has occurred. Patients subjected to total adrenalectomy usually require cortisone 25 to 50 mg., DCA 2 mg., and sodium chloride 3 to 6 gm. daily. The tendency toward progressive weight gain with such a regimen makes it desirable to explore the use of other agents and schedules of dosage.

Among the 96 surviving patients the following late sequelae have appeared: Intolerance to cold (19), mild Raynaud's phenomenon (18), pigmentation of the skin (21), failure of ejaculation in males (15). Among 15 patients showing persistent and marked elevations of blood pressure postoperatively, 7 have shown improvement while receiving such drugs as protoveratrine, hydralazine, and reserpine.

It is emphasized that this is an experimental approach, which cannot yet be recommended as a treatment for hypertension. A well integrated medical, surgical and laboratory team, and close observation throughout the entire postoperative course are prerequisites for such a study. As in the case of sympathectomy, we cannot predict which patients will respond with improvement, nor can we explain why certain patients with adequate renal function have failed to improve after operation. A few patients whose blood pressure responses were excellent following operation have eventually succumbed to vascular accidents.

TRANSACTIONS & STUDIES

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Biochemical Explorations of Certain Disturbances of Carbohydrate Metabolism[1]

By DeWITT STETTEN, Jr.[2], M.D., PH.D.

Mr. Chairman, Fellows of the College of Physicians of Philadelphia, Ladies and Gentlemen:

I am deeply honored by the selection of my name as the recipient of the Alvarenga Award, and I should like to take this opportunity to express to your committee my appreciation of this honor which has been bestowed upon me. I should like also to acknowledge my indebtedness to the numerous colleagues and collaborators with whom I have had the privilege of close association and whose contributions to problems of mutual interest form a basis for this evening's discussion.

In an interesting book of a few years ago, Dr. Wayne Umbreit (1) pointed out the strong analogy between the plotting of metabolic pathways and cartography, the science and art of drawing geographical maps. The purpose, in both cases, is to reduce a body of knowledge to simple schemes which can be represented on simple coordinates. Underlying the construction of such a map or scheme there is required a vast amount of exploration and discovery designed to invade and diminish the *terra incognita* and to define boundaries and routes with increasing precision.

Early exploration is tentative and empirical. Such was the first exploration with which we need concern ourselves tonight, the injudicious tasting of a urine sample by Thomas Willis, of arterial circle fame. In the middle of the 17th century he described the sweet taste of the urine of certain diabetic patients, thereby distinguishing diabetes mellitus from diabetes insipidus and indicating that the former disease was a disturbance of carbohydrate metabolism. The accredited father of biological chemistry is Lavoisier who, a few years before the establishment of this society, had demonstrated that the phenomena of combustion and of total gaseous metabolism were essentially identical. Your society was founded in 1787, and seven years thereafter, Lavoisier was put to death by decapitation, a fate fortunately uncommon among biochemists but not unique among explorers, to wit, Balboa and Sir Walter Raleigh.

Time does not permit us to pay homage to all the explorers nor to describe all the voyages of discovery in the vast and turbulent sea of disturbed carbohydrate metabolism. Among the landmarks were the discovery of glycogen,

[1] Alvarenga Prize Lecture XIV (Award XLIX), College of Physicians of Philadelphia, 6 October 1954.

[2] Associate Director in Charge of Research, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Department of Health, Education and Welfare, Bethesda 14, Maryland.

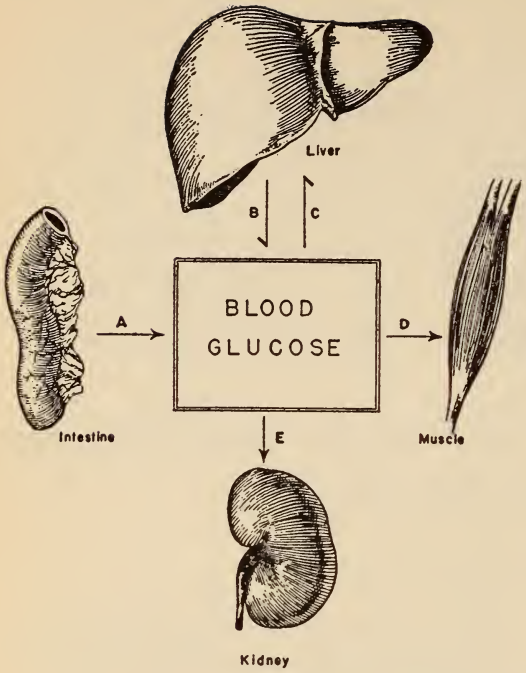

FIG. 1. Sources and Fates of Blood Glucose.

the animal storage form of glucose, by Claude Bernard, the studies of the configurations of the sugars by Emil Fischer and others, the demonstration of the relationship of the pancreas to carbohydrate metabolism by von Mehring and Minkowski, the isolation of insulin by Banting and Best, and the elucidation of the pathways of glucose metabolism by Embden, Meyerhof, the Coris, and a host of other workers. It is against this background that our map must be drawn.

Precisely what is meant by a disturbance of carbohydrate metabolism? How is such a situation recognized? In many cases the recognition of a disturbance of carbohydrate metabolism depends upon the observation of an abnormal concentration of glucose in the blood. This is a significant finding only because of the fact that under given circumstances, in the normal subject, the concentration of blood glucose is known to fluctuate within relatively narrow limits. The blood sample to be analyzed may be derived from a fasting subject, from a subject who has recently received glucose by mouth or by vein, or from a subject who has been given epinephrine or insulin. In each of these cases we know, from previous experience, within what limits the normal blood glucose concentration should fall. If it falls outside these limits, a disturbance of carbohydrate metabolism may be said to exist.

It is clearly recognized today that the concentration of glucose in the blood remains constant within fairly narrow limits, not because glucose is chemically inert but rather because there normally exists a remarkably fine balance between the rate at which glucose is entering the blood stream and the rate at which it is leaving the blood stream. Glucose enters the blood by the portal absorption of products of digestion in the intestinal tract, but this is not the sole source. An additional source is from liver, and to a lesser extent kidney and possibly other organs, which can generate glucose from glycogen as well as from non-carbohydrate precursors. Glucose leaves the blood stream to be broken down or polymerized in most of the tissues of the body, especially in the skeletal musculature. Under abnormal circumstances, glucose may be lost via the urine to a very appreciable extent, although in the normal subject this loss is trivial.

Fig. 1 represents crudely these relationships. In our map-making analogy, this diagram is a sort of compass rose, and indicates only the directions which may be followed. The blood glucose concentration is here represented as a resultant of several vectors. The process represented by each of these arrows is subject to clinically observed disturbances and we may therefore review with profit each of these processes.

The bulk of digestible dietary carbohydrate is the polyglucoside, starch. The gastrointestinal hydrolysis to which this is normally subjected depends largely though not entirely upon contact with pancreatic amylase. Consequently any disease process which interferes with such contact will interfere with the dietary source of blood glucose. The diarrheal diseases as well as disturbances of the external secretion of the pancreas will result in the appearance of undigested starch granules in the

feces reflecting the loss of carbohydrate which would otherwise be useful to the organism. Quite obviously fasting will likewise deprive the organism of this important source of carbohydrate.

Even in the presence of adequate digestion, ingested carbohydrate may fail to contribute normally to the blood glucose. The transport of glucose across intestinal mucosa is an active rapid process in the normal subject. It has long been known that the intestinal mucosa performs work upon glucose and pushes it, so to speak, from the luminal to the vascular border. Whereas the exact nature of this work is unclear, it is widely held to involve phosphorylation of glucose in transit at the expense of energy stored as adenosine triphosphate. Interference with this mucosal function is seen in sprue and is reflected in the clinical finding of a normal intravenous glucose tolerance test in the face of a failure of the blood glucose concentration to rise after oral glucose administration. An experimental situation which mimics, in this regard, the clinical picture of sprue is the topical poisoning of the intestinal mucosa with phlorhizin.

A second source of blood glucose, which supplements the dietary source, is from the breakdown of glycogen to glucose as well as the synthesis of glucose from a variety of precursors. As will be discussed more fully subsequently, this involves in essentially all cases the enzyme-catalyzed hydrolysis of glucose-6-phosphate, a process especially readily carried out in liver, although other organs, such as kidney, undoubtedly contribute. Situations in which this source of blood glucose may be deficient are numerous. It is clear that in the absence of liver glycogen, no glucose can arise from hepatic glycogen breakdown. This may occur, for example, after fasting, or in the thyrotoxic organism. Of greater interest are disease states in which glycogen, though abundantly present in liver, fails to contribute to blood glucose. The glycogenosis of von Gierke's disease is clinically demonstrable by the failure to elicit the expected hyperglycemia after epinephrine administration. This agent, which normally favors the breakdown of glycogen, fails to do so in this disease for reasons which will be considered in some detail later.

The immediate precursor of glucose of hepatic origin is glucose-6-phosphate. This arises not solely from glycogen, but also from a variety of compounds including most of the amino acids. Interruption of this latter pathway probably occurs in Addison's disease, whereas an exaggeration of this contribution is induced by administration of 11-oxycorticosteroids. This mechanism is the one referred to as "glucose overproduction" and may be accompanied by excessive urinary nitrogen loss, insofar as carbon, but not nitrogen, of amino acids is being used for glucose synthesis.

Thus far disturbances in the sources of blood glucose have been considered. Let us now survey briefly the fates of blood glucose and diseases which influence them. Glucose may be consumed by all tissues but its consumption by liver and by striated muscle come into particular prominence here. Of importance is the striking fact that, although a very reactive compound in the test tube, glucose undergoes only one known chemical reaction in the body, namely phosphorylation to yield glucose-6-phosphate. It is from this latter product that the numerous metabolic fates of glucose stem. The generation of glucose-6-phosphate within the cell from glucose of the blood is a transformation subject to delicate hormonal regulation, and the rate of this process critically affects not only the level of blood glucose but also the nutrition of the tissues. As a first approximation insulin may be said to favor this net transformation whereas the secretions of the anterior pituitary gland interfere with it. The rise in blood glucose concentration in diabetes is thus referable to an impediment in the consumption of blood glucose by the cells. The hypoglycemia of hyperinsulinism is a consequence of excessive consumption of glucose, especially by muscle cells. It should be noted in passing that glucose, although it enters muscle cells readily enough, does not leave muscle cells as such to any appreciable extent. In this regard it is to be differentiated from

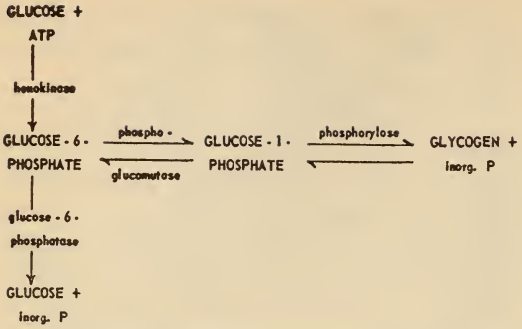

FIG. 2. Pathways of Glycogenesis and Glycogenolysis.

liver, which is both a consumer and a producer of blood glucose.

The last fate of glucose to be considered on this diagram is its excretion by the kidney. Urinary loss of glucose is trivial in the normal subject, even after massive glucose feeding. It does occur, however, under two well recognized clinical circumstances. One of these is hyperglycemia in excess of the renal threshold, as may occur in diabetes, in response to epinephrine, or following intensive corticosteroid administration. The other is a lowered renal threshold as is seen in Fanconi's syndrome or as may be produced experimentally by phlorhizin poisoning.

The discussion thus far has dealt with the directions which abnormalities of blood glucose concentration can take. As will be seen, diseases are known which influence each of the vectors here presented (*Fig. 1*). I should like to devote the remainder of the time to a more detailed consideration of certain of these arrows.

The formation and destruction of glycogen has until recently been indicated by the series of reactions shown in *Fig. 2*. Glucose is initially phosphorylated in position 6 by adenosine triphosphate, and the product formed, glucose-6-phosphate, is reversibly isomerized to glucose-1-phosphate. The sugar moiety of this product is then reversibly added on to a preformed glycogen molecule, with the elimination of inorganic phosphate. Growth of the glycogen molecule results from this process of accretion. The intracellular decomposition of glycogen is initiated, according to this scheme, by phosphorolysis, rather than hydrolysis, and among the fates open to the hexose phosphate arising in liver is hydrolysis to glucose by the action of a specific glucose-6-phosphatase. It is the lack of this enzyme in muscle which renders this tissue incapable of returning glucose to the bloodstream.

It should be noted that glucose-6-phosphatase, although of importance in liberating glucose, does not participate in glycogen synthesis in any way. The finding by Cori and her collaborators (2) that this enzyme is deficient in the livers of certain patients suffering from von Gierke's disease offers a very satisfactory explanation of the glycogenosis that is encountered. Whereas all the steps leading to glycogenesis are intact in such livers, an essential step in the breakdown of glycogen to glucose is now inoperative. With an important fate of hepatic glucose-6-phosphate excluded, the remaining reversible reactions are pushed to the right and glycogen must accumulate. It may be mentioned in passing that an action of epinephrine, as well as of glucagon, the product formed by the α-cells of the islets of Langerhans, is to favor the activation of phosphorylase (3), and this action is presumably related to the glycogenolytic effect of these two agents.

A more detailed understanding of the structure of glycogen has led to a more complete picture both of glycogen turnover in the normal and of glycogenosis in the diseased sub-

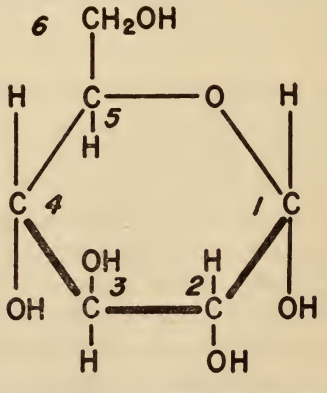

FIG. 3. Formula of α-D-Glucopyranose.

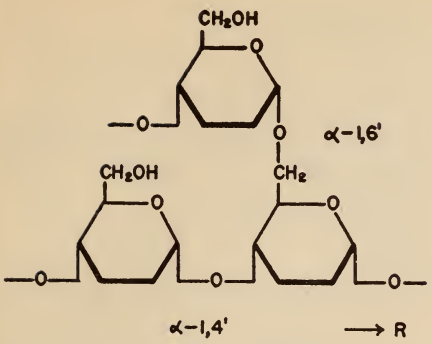

FIG. 4. 1,4 and 1,6 Glucosidic Bonds.

FIG. 5. The Structure of Glycogen, according to Larner and Cori.

R, reducing end of molecule.

⊙, ⊖, ◒, glucose units removed by the first, second, and third digestions with phosphorylase, respectively.

●, glucose unit split off as free glucose from 1,6 linkage by amylo-1,6-glucosidase.

(Figure from McElroy and Glass. Phosphorus Metabolism, vol. 1, p. 667, 1951. Courtesy of Johns Hopkins Press, Baltimore, Md.)

ject. The formula of glucose, represented according to current conventions in *Fig. 3*, shows the numbering of the several carbon atoms. In glycogen and starch, the common linkage is an oxygen bridge, termed a glucosidic bond, between carbon 1 of one glucose and carbon 4 of its neighbor (*Fig. 4*). If this were the unique link, these polysaccharides would be long unbranched chains of glucose residues, and indeed this is the case in the starch, amylose. In amylopectin, and to a greater extent in glycogen, the structure is a branched arboreal one, and this is a consequence of the occurrence of 1,6 bridges in addition to 1,4 bridges. At each point of branching there is one glucose residue which is bound to three other glucose residues, at its 1,4 and 6 positions. These branch points arise as a consequence of the action of a branching enzyme which generates 1,6 links at the expense of 1,4 links. The latter arise directly from the action of phosphorylase.

In their study of these structural relationships, the Coris and their collaborators found that by use of appropriate enzymes it was possible to dissect the glycogen molecule in a neat, step-wise fashion (4). The attack of pure phosphorylase plus inorganic phosphate upon glycogen yields glucose-1-phosphate from the peripherally situated unbranched terminals until a point of branching is approached (*Fig. 5*). The resultant phosphorylase-refractory polysaccharide, called a limit dextrin, is rendered again phosphorylase-sensitive by the action of a specific muscle enzyme, amylo-1,6-glucosidase, which hydrolytically splits off the exposed glucose residues that are in 1,6 linkage. By the alternating attack of these two enzymes the glycogen molecule may be peeled like an onion, and the composition of each successive layer can be studied. Such a dissection is represented in *Fig. 6*, where P-1, P-2 and P-3 represent the sugar split off by each of three successive treatments with the enzymes described above, and LD-3 is the limit dextrin remaining after the third treatment.

In a study currently under way in collaboration with Dr. Marjorie R. Stetten, the mechanism of glycogen turnover in the normal animal has been explored by the device of injecting glucose labeled with carbon-14 into normal animals and studying the distribution of radioactivity in the several tiers within the glycogen molecules recovered from their tissues. The results of such an experiment are shown in *Fig. 7*. Six hours after injection of glucose-C^{14} intravenously into a rabbit, the animal was killed, muscle glycogen was isolated, and this product was in turn subjected to three degra-

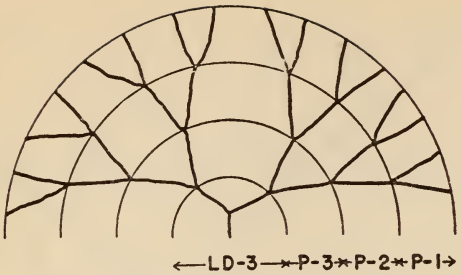

FIG. 6. The Tiers of Glycogen (see text).

dation steps. Here are plotted the relative specific activities of the glucose residues in each layer versus the fraction of glucose liberated by each enzymatic treatment.

The first evident conclusion is that the radioactivity is not uniformly distributed throughout the molecule. The outer tier is by far the most radioactive, and radioactivity decreases as one progressively enters the molecule. The central limit dextrin, LD-3, is very poor in carbon-14.

The time course of this distribution of radioactivity has also been studied. In *Fig. 8* are shown the results of studies on the liver glycogen of rats, employing similar techniques. Whereas the distribution of isotope in liver glycogen 6 hours after administration of glucose-C^{14} resembles qualitatively that seen in the previous figure, with the bulk of the isotope at the periphery, with the passage of time this situation changes and by the 48th hour the highest concentration of C^{14} is found in the center of the molecule, the lowest radioactivity at the periphery.

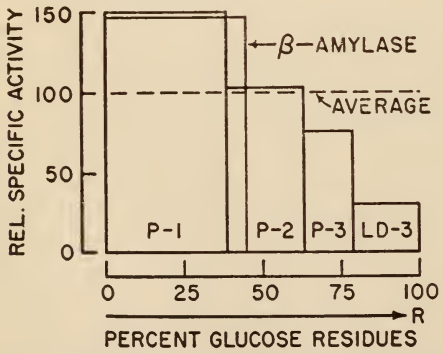

FIG. 7. Distribution of C^{14} in Tiers of Rabbit Muscle Glycogen 6 Hours after Injection of Glucose-C^{14}.

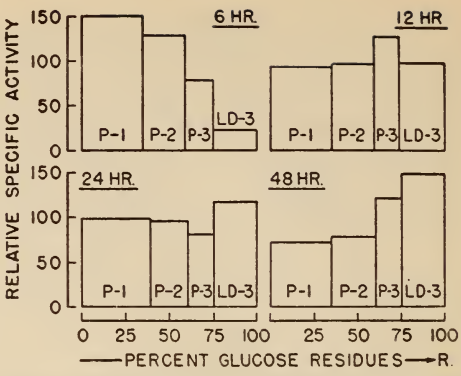

FIG. 8. Distribution of C^{14} in Tiers of Rat Liver Glycogen at Various Times after Injection of Glucose C^{14}.

From results such as these it is possible to offer a preliminary reconstruction of the events involved in glycogen turnover. It is clear that glycogen turnover does not involve the simple replacement of a pre-existing glycogen molecule by a newly formed glycogen molecule. Rather it appears that continuous and rapid replacement of glucose residues situated at the periphery of the molecule is taking place. This is undoubtedly a function of phosphorylase activity. More slowly, presumably as a consequence of the action of the branching enzyme, glucose residues, initially in peripheral tiers, find their way into more centrally located tiers. Since glycogen is in a steady state, it must continuously be breaking down as it is being built up. This process requires the collaborative efforts of phosphorylase and the debranching enzyme, amylo-1,6-glucosidase. The nature of the arboreal structure of glycogen is a function of the relative activities of at least the three enzymes, phosphorylase, branching enzyme and debranching enzyme. It is of interest that in those patients suffering from glycogen storage disease studied by Cori (2) in whom liver glucose-6-phosphatase was found to be normally present, striking deviations from the normal branching pattern of glycogen were detected.

Clinically the most important disturbance of carbohydrate metabolism is diabetes. We may summarize the metabolic defect in this disease by the statement that most products which

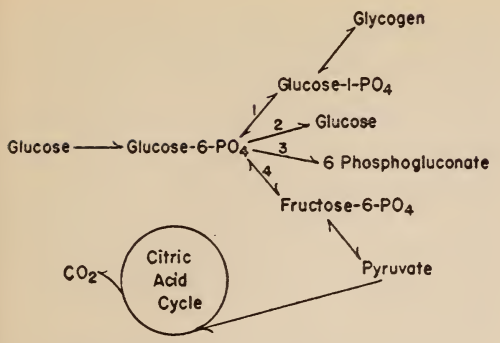

FIG. 9. Fates of Glucose-6-Phosphate.

normal muscle or normal liver generate at the expense of glucose, are formed to a lesser extent by the corresponding tissues of the diabetic. The normal animal continuously generates, from blood glucose, a host of products including glycogen, lactic and pyruvic acids, CO_2, fatty acids and many other compounds. All of these are formed to a lesser extent in certain tissues of the diabetic animal than in those of the normal. This generalization, like many others, is subject to certain limitations in that not all tissues are equally susceptible to diabetes. Thus whereas the defects just mentioned are readily demonstrable in liver and muscle derived from diabetic animals, they are not apparent in brain, kidney or myocardium.

The very fact that essentially all of the fates of glucose are impeded in the diabetic suggests that the defect which results from hypoinsulinism occurs in the early stages of glucose utilization. The basis for this suggestion, indicated in *Fig. 9*, is that whereas only one chemical fate of glucose, phosphorylation to glucose-6-phosphate, is known to occur in the animal, glucose-6-phosphate has several fates open to it. As mentioned earlier, it may go to glycogen via the 1-phosphate or it may be hydrolyzed to glucose. Again it may be oxidized to 6-phosphogluconic acid or it may be isomerized to fructose-6-phosphate. Fructose-6-phosphate initiates a sequence of catabolic reactions which is known in its entirety as the glycolytic, or Embden-Meyerhof sequence. 6-phosphogluconate initiates another catabolic pathway, a subject of more recent exploration, sometimes called the "oxidative" pathway or the "hexosemonophosphate shunt" (5). Recent studies in collaboration with Dr. Bloom and other members of our group have revealed that whereas in muscle the glycolytic pathway, via fructose-6-phosphate, appears to be the sole route of glucose catabolism, in liver only about half of the glucose is thus catabolyzed, while the remainder is oxidized via 6-phosphogluconic acid.

Returning to the consideration of the defect in diabetes it will be seen that if essentially all fates of glucose are interfered with in this disease, the plausible site of the defect is at or prior to the point of divergence of pathways. If traffic passing down each of several divergent roads is observed abruptly to cease, one may legitimately suspect that a road block occurs at a point prior to the divergence.

Two events precede the divergence of pathways of glucose catabolism in mammalian tissues (*Fig. 10*). The first of these is the entry of glucose into the cell from the extracellular space. The second is the hexokinase-catalyzed phosphorylation to yield glucose-6-phosphate. At one time it was considered likely that these two events were essentially the same phenomenon, but today this view is no longer tenable. Evidence has been proposed implicating each of these events as being insulin-sensitive.

Some years ago Cori and his collaborators found muscle hexokinase to be subject to an inhibition (6). The inhibitor, presumably aris-

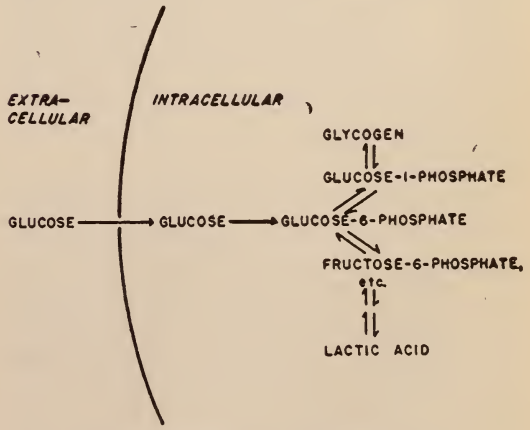

FIG. 10. Possible Sites of Insulin Action.

ing in the pituitary may be the same material which Bornstein (7) has demonstrated in the plasma of diabetic animals, lipoprotein in nature. Insulin, devoid of any direct effect upon hexokinase, appears to release hexokinase from this inhibition. According to this view it is the phosphorylation step which is sensitive to insulin.

Contrasting results have come from Levine's laboratory (8). The evidence presented by these workers quite clearly points to impaired passage of glucose across cell membranes as the primary defect in the metabolism of diabetics. The inability of several sugars to enter the intracellular compartment unless insulin is supplied has been demonstrated and since some of these sugars are not believed to undergo phosphorylation in mammalian systems, a mechanism of impaired phosphorylation is insufficient to explain the results. Strong supportive evidence for the view that insulin influences the transposition rather than the initial transformation of glucose has also come from the work of Park (9).

A partial but ingenious explanation has recently been offered by Keston (10). He points out that glucose exists as a mixture of at least two anomeric modifications, α and β. Mutarotation, which is the interconversion of these two, a slow spontaneous process, is catalyzed by an enzyme, mutarotase, now shown to occur in certain mammalian tissues. If it be assumed that one but not the other anomer is free to cross cell membranes, then it may be the rate of mutarotation which limits the rate at which glucose enters cells. According to this view insulin may be supposed to influence mutarotation of glucose in a favorable fashion.

Many defects other than those directly associated with carbohydrate metabolism as such have been demonstrated in the diabetic animal. Some of these, such as the retinal and renal changes, are today not susceptible of neat explanation. Others, such as the ketosis, the impairment of hepatic lipogenesis, the hindered synthesis of proteins from amino acids, can tentatively be explained. The normal synthesis of fatty acids or of peptide bonds requires the coincident liberation of energy and for this energy the tissues of the body require in turn an active catabolism of sugars. The retardation of glucose utilization occurring as a consequence of hypoinsulinism may be pictured as depriving the liver and other tissues of the extra chemical energy needed to permit the synthesis of protein and body fat to proceed at optimal rate.

In a very abbreviated fashion I have tried to bring the story up to the very latest explorations. But explorations are a speculative business, whereas map-making is or should be an exact science. From time to time careful surveys are required in order to check and correct existing maps and to bring into proper perspective recent discovery.

As was the case with primitive geographical maps, there are discrepancies in our present picture of carbohydrate metabolism and its disturbances. This much, however, is certain. In nature there are no discrepancies, and those which appear in our charts and maps are therefore apparent and not real. They represent either erroneous observation or incomplete information. We may take it as a goal, always to be approached though perhaps never to be attained, that when all the facts are in and are properly assessed, all apparent discrepancies on the maps will necessarily be resolved.

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The Chemical Pathology of the Virus-Infected Cell[1]

By SEYMOUR S. COHEN,[2] PH.D.

It is a great honor to be asked to address the College, and I am pleased to be afforded the opportunity to contribute to the furtherance of the aims of this institution. Originally the Thomas Dent Mütter Lectureship was established to provide a course of lectures in surgical pathology. In recent years the College has been addressed on several occasions on other subjects, which have included such matters as infectious disease and virology. I am particularly honored to continue this line of discussion in the footsteps of the late Dr. Balduin Lucké, and of my own chief, Dr. Joseph Stokes, Jr.

In this lecture I shall describe some recent efforts to understand the pathology of infection at the level of the single cell. We shall see that the biologist and chemist working in this area have much in common with the surgeon, that precise dissection is also our business. In the dissection of the virus-infected cell, however, the chemist adds the fourth dimension of time to his studies. We shall see that he is not satisfied to probe ever more deeply into less and less, but that he must do this from minute to minute as well. What is there at one instant, disappears in the next, and curiously enough a virus comes into being where there was none before.

The fact of the matter is, that a careful regard for quantitation and dimensions such as time has been the core of all advance in this field for the past fifteen years. The experimental requirement that the effects of virus infection should be sought from moment to moment within the volume of the infected cell has produced a revolution in the thought and progress of virology. An experiment which sets its focus in this way demands cells which may be infected at a given instant under defined environmental conditions. This requirement eliminates intact hosts as key test systems and has stimulated work on the growth of cells in *in vitro* systems. Given suitable suspensions in appropriate media of cells of bacterial, plant, or animal origin, one may add virus and study problems of attachment, penetration, and cell change at a morphological or chemical level, as well as the liberation of virus following multiplication. If the cell suspension is not homogeneous or incompletely infected, cytological abnormalities may be sought by microscopic examination of the infected cells. Histochemical technique is also useful in these types of systems, since the histochemist examines single cells. It is appropriate to mention at this point that in the last three years the recent spurt in our knowledge of poliomyelitis has occurred only as a result of such an experimental approach. As you know, the discovery of the growth of the virus in tissue cultures by Enders and his collaborators, and the application of this simple fact, have led to great advances in diagnosis and in vaccine production.

The biochemist must have a homogeneous suspension of cells which he can infect in toto, so that his analyses will not be confused by the substances derived from uninfected cells. To obtain such a system, the biochemist must be able to add a suitable number of virus particles to a known number of cells in a manner such that adsorption and infection will proceed as required. The biochemist working in virology must then be familiar with some elements of statistics and with the technique

[1] Thomas Dent Mütter Lecture LXVII, College of Physicians of Philadelphia, 1 December 1954.

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FIG. 1. Escherichia coli infected by T2 bacteriophage. The tail of a phage particle is 0.1 micron in length. (This electron microphotograph was taken by Dr. T. F. Anderson of the University of Pennsylvania School of Medicine.)

and principles of the cell biologist and virologist as preconditions for study in this field. It has been noted that present day virology cuts across all disciplines, and in this area of research it is only slightly less commonplace to find the biologist becoming a chemist than to find the chemist talking about cells.

At the inception of this revolution in methodology, i.e., the concentration of biologist and chemist upon virus-infected cells, a group of investigators of the most diverse backgrounds, physicists, chemists, geneticists, etc., agreed some ten to fifteen years ago to sharpen their tools and wits upon a single system of virus and host. The host in this system consisted of the lowly bacterium, *Escherichia coli*, which could be prepared as single dispersed cells in defined media; these bacteria can be manipulated and counted without difficulty. A group of seven viruses or bacteriophages were available, and relatively simple techniques permitted their quantitative assay by the plaque counting technique, and their isolation, by the well known procedure involving differential centrifugation.

In *Fig. 1* may be seen a virus called T2 attached to its host bacterium. The T-even viruses, i.e., the T2, T4, and T6 bacteriophages, with which most of the work in my laboratory has been done, are structurally similar to other phages, in that they are all tadpole shaped. The head, which is enclosed by a membrane, contains the genetically active substance of the virus. This critical substance is injected into the host cell through the needle-like tail, by means of which the virus is adsorbed to the cell. The length of the tail varies from species to species and in T3 and T7 this structure has only recently been discovered, since it is very short. The tail-first adsorption to the bacterium, observable in the Figure, was first observed by Dr. T. F. Anderson. Certain isolated substances, such as the receptor substances of the bacterium, can trigger the release of the innards of virus, which leaves the head via the tail as long spaghetti-like threads.

In collaboration with Dr. Anderson, we isolated and analysed the T2 and T4 phages, and demonstrated the presence of protein and a large amount of a deoxyribose nucleic acid (1). This latter type of substance, which is an important chromosomal constituent and which has been shown in some microorganisms to bear genetic information, constitutes about 40% of the dry weight of the virus. We have isolated it from virus as a high molecular polymer which forms very viscous solutions in low concentration. This substance, which is commonly referred to as DNA, contains all of the phosphorus of the virus; this virus, therefore, lacks a very important nucleic acid, ribose nucleic acid, which is present in all cells. The phages lack a wide array of other phosphorus-containing materials, such as phospholipids, soluble coenzymes, and the nucleotides essential to metabolic activity in typical cells. From this equivalence of DNA phosphorus and total phosphorus then, it is evident that the viruses are structurally and metabolically incomplete, as compared to cells; this fact in itself may explain the dependence of the bacterial viruses, and indeed all known viruses, upon their hosts for the multiplication of the virus.

When the T-even phages infect *E. coli*, the bacterium loses the power to multiply although

the metabolism of the cell continues at about the same intensity as it did before infection (2). Such an effect was particularly evident in the respiration of the cell, which continued unchanged up until the moment of lysis and virus liberation. We found very early, however, that by far the largest part of the metabolism was no longer directed to the synthesis of host substance but rather was redirected to the synthesis of virus. The infected cell ceased to make enzymes, proteins and ribose nucleic acid for its own growth, but diverted its uptake of metabolites to the channels essential for the synthesis of virus protein and DNA.

Such an effect is particularly striking in examining nucleic acid metabolism. Most of the phosphate entering the normal bacterium is directed to the formation of ribose nucleic acid. On infection the accumulation of this substance stops and the phosphate which would normally end in this substance is diverted to form DNA at a greatly increased rate. The DNA formed is exclusively virus DNA. Its synthesis begins a few minutes after infection, and continues at a constant rate throughout the interval of virus synthesis.

It is evident that this system represents a most severe type of parasitic relationship. The virus does not convert metabolically active host substance into virus. The enzymes of the host are conserved for purposes of virus production, and all the energies of the host are subordinated to that end. It is only when the cell is stuffed with virus to the bursting point that this synthesis stops, that the cell indeed bursts and liberates virus ready to attack new host cells. How does the infecting virus particle assume control in this way? What are the special properties which permit the flea (10^{-15} gm.) to pull the elephant (10^{-12} gm.) around by the nose?

The metabolic pathways of all cells of bacterial or of higher types, have many points of interaction. The structures of a cell contain hyphenated compounds; they are made of many nucleo-proteins, of lipo-proteins, muco-proteins, etc., which are themselves integrated into larger structural units. It was reasonable to suppose that a block in the formation of one key constituent would have serious repercussions in the most diverse syntheses, and that a block in some component of nucleic acid, for instance, might prevent the synthesis of host nucleic acid, its contiguous protein, the whole particle in which the nucleoprotein is present, and finally the synthesis of enzymes and structures made at the particle. This seemingly simple hypothesis, that the profound reorientation of cellular metabolism may be explained at the molecular level in terms of the synthesis or lack of synthesis of a very few critical compounds, is supported by the analysis which I shall now describe.

Parenthetically, I may remark that the most direct progress in science is afforded by a two-fold process. It is desirable that the proper questions be asked, questions which bear a close relation to the reality of the phenomenon under investigation. Secondly, it is helpful if experiments are performed which actually answer these questions. Very often, as is well known, questions may be asked which do not really describe the event being analysed. In some fortunate instances, the experiments performed may give answers to the questions one should have asked but didn't. Most often, I suppose, important information on a given problem comes from experiments which were designed to answer apparently unrelated questions, and indeed most important answers do seem to have arisen in all of these indirect ways*.

The nucleic acid and the protein outer skin of T2 phage may be differentially labelled with P^{32} and S^{35} respectively. Hershey and Chase (3) showed that when bacteria are in-

* I would point out that the phenomena of virus parasitism and multiplication which I shall describe were only partly unraveled in my laboratory. The social process in this field is such that many laboratories have contributed their thought, information, and discoveries rapidly and efficiently to the common search. And of course in my own experimental work I have worked and collaborated with many individuals without whom only a small fraction of our observations could have been made.

fected with differentially labelled virus, the protein outer skin, consisting of tail and head membrane, remains outside of the bacterium; these structures are the syringe for the genetic material. The contents of the head, containing the DNA of the virus, are injected into the bacterium and provide information and models essential for the synthesis of more virus. It is by no means clear whether DNA is injected free of protein or not. Ingenious experiments by Stent have indicated that the genetic information which may be carried initially by the DNA may be transferred very early to a non P-containing constituent which presumably is protein.

Some years ago we showed that infected cells contain desoxyribonuclease which can degrade phage DNA. Other data have indicated that the cell contains active phosphatases as well, which can degrade nucleotides to their dephosphorylated products, the nucleosides. Kozloff (4) has observed that infection liberates the DNAase which normally has only slight activity in the growing bacterium. It appears that the nuclease is inhibited by ribose nucleic acid, and this inhibition is released in some way as a result of infection. The desoxyribonuclease then proceeds to fragment the DNA of the bacterial nucleus.

How does it happen that the DNA injected from a single virus particle evades the degrading activity of the host enzymes which destroy the host DNA? As shown by various workers, the fragments of host DNA are quite small and are re-utilized in the supply of materials for the synthesis of the DNA of infecting viruses. We have shown that virus DNA, unlike the DNA of numerous cells, is far more enzyme resistant and although partially degraded by nuclease and phosphatase, enzyme resistant moieties appear to be selectively preserved (5).

That the virus DNA contained a built-in survival mechanism which also conferred biochemical specificity upon the virus first became apparent as a result of the work of Dr. G. R. Wyatt and myself on the bases of virus nucleic acid (6). It was discovered in the course of analysing the T-even group of viruses that they all possessed a unique base. Although the base composition of the viruses appeared to be identical, they contained a pyrimidine which had never previously been observed, 5-hydroxymethylcytosine (HMC). This substance in effect replaced the pyrimidine base, cytosine, which had been found in all other nucleic acids. Thus, the bacterial ribose and deoxyribose nucleic acids both contained cytosine and lacked HMC, whereas the virus contained HMC and lacked cytosine. Thus for the first time it has been found that a virus contains a building block not found in significant amount in its host.

The enzyme-resistant polynucleotide fraction of virus DNA is greatly concentrated with respect to its HMC content alone, and we have suggested that the structural relations of this moiety provide the basis of the survival of the virus DNA (5). It could be supposed that within the infected cell, the virus DNA is spatially separated from the nucleases, etc. This appears unlikely since virus DNA which is injected naturally into the bacterium is also partially degraded to low molecular fragments.

Following the isolation of free HMC, other compounds containing this substance have been separated from virus nucleic acid (*Fig. 2*). We have isolated a nucleoside containing 1 mole of deoxyribose per mole of HMC, thus accounting for about 90% of the total HMC (5). Several types of nucleotides of HMC have been found, depending on the procedure employed in the degradation of

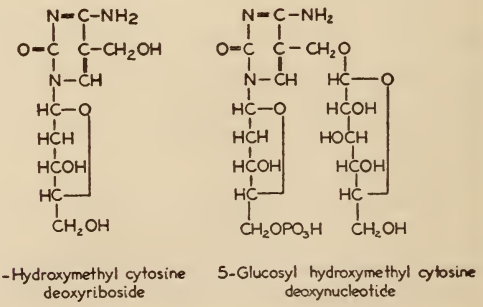

FIG. 2. A nucleoside and nucleotide of 5-hydroxymethyl cytosine.

virus DNA. By acid hydrolysis a nucleotide or diphosphate ester of the nucleoside has been isolated (7). Following enzyme degradation, two nucleotides of HMC have been isolated (8). Both appear to contain phosphate at the 5′ position, whereas one of these appears to contain glucose substituted at the hydroxymethyl group. The glucose-substituted compound is quite resistant to phosphatase. Thus not only does the virus DNA have a new base, but it also contains a hexose which has never previously been seen in a nucleic acid. The existence of a hydroxymethyl group on the pyrimidine makes possible the addition of the hexose, which hinders the cleavage of the phosphate on the deoxyribose portion of the molecule.

After the insertion of the phage substance into the bacterium, protein synthesis continues (2) during the destruction of the bacterial nucleus and DNA. Several minutes after the degradation of the DNA has begun, the synthesis of virus DNA may be detected. Thus one may follow the disappearance of host cytosine and the formation of HMC in the DNA fraction of infected cells (9). Dr. L. Weed and I have demonstrated such a transformation by isotopic methods and have shown that the β-carbon of serine may form the carbon of the hydroxymethyl group (5).

With the formation of this compound, virus synthesis is unquestionably on its way. The infected cell is now committed to the synthesis of viral materials and appears unable to make host enzymes or either of the host nucleic acids. How can we picture this phenomenon?

At the present time, it seems possible to explain the reorientation of metabolism entirely as a consequence of the synthesis of HMC and its structural relations (5). In studies of pyrimidine utilization in normal and infected cells, it was observed that HMC and derivatives are stable, almost inert compounds, even as is the virus DNA. Thus free HMC, unlike cytosine, is not deaminated by the cytosine deaminase of *E. coli* or of yeast, and does not fulfill the pyrimidine requirements of various bacterial mutants. The hydroxymethyl group, once added, removes cytosine from metabolic routes leading to growth.

However, free HMC is inert even in infected cells and it appears more likely that this compound is handled as the nucleoside or nucleotide. The HMC nucleoside is metabolized slowly by infected cells but it also does not fill pyrimidine requirements, i.e., it will not lose its hydroxymethyl group. It is deaminated however, albeit far more slowly (2–3%) than is cytosine deoxyriboside, to the hydroxymethyl uracil deoxyriboside, which also appears to be a dead end. Thus hydroxymethylation of cytosine or uracil, in whatever form, serves as a trap for these bases. The formation of glycosyl nucleotides in virus DNA removes the pyrimidines still further from the metabolism of the bacterium. The whole process is capped by enclosing the DNA in a membrane within the head of the phage. Infection in some way establishes the conditions for this metabolic trap and cytosine and uracil then become unavailable. In the absence of cytosine, host ribose nucleic acid and host DNA can no longer be made. The structures can not be built which contain these substances; these include the chromosomes and numerous enzyme containing particulates of the bacterium. Dr. D. B. McNair Scott and I have studied transformations in the balance of pathways of carbohydrate metabolism and it has been concluded that the disturbances noted in these systems are but secondary consequences of the central disturbance in nucleic acid metabolism (9). It can be seen that the survival, the specificity, and the parasitic efficiency of the virus all appear to turn on the relatively minor alteration of structure of a single building block. It seems possible to refer to HMC as the key to the molecular basis of parasitism in this system of cell infected by the T-even phages.

There is very little known about the details of the steps leading to HMC synthesis and to its incorporation into DNA. The duplication process, the formation of protein and of intact

virus particles, the lytic process are similarly quite obscure and are problems which will require extensive exploration. At the outset we may confidently make the following generalizations; (1) that research on these unsolved problems will merge with the interests and research on systems of more practical interest, and (2) that there are great surprises in store for us.

I should like to conclude by describing a number of observations which began in our studies on infected cells, and have completely distracted us for the last year and a half.

If the formation of HMC leads to such extreme distortion of the growth process, why are there normal cells? It would appear likely that the formation of HMC does not occur normally or occurs at an insignificant rate. Virus infection may be supposed either to introduce the enzyme or cofactors essential for hydroxymethylation or to destroy inhibitors which hold the system in check. In an experiment with a mutant requiring the pyrimidine, thymine, for normal growth, Miss Hazel Barner and I observed that infection of the mutant with T2 phage in the absence of exogenous thymine resulted in the synthesis of thymine, as well as of HMC, leading to the synthesis of virus DNA and virus. In this instance an infected cell became capable of synthesizing two pyrimidines which it could not previously make (10). We have found that the uninfected cell can make a very low level of thymine, about 2 to 4% of that normally required for growth, and we are led to believe that the thymine-synthesizing system is normally suppressed in this cell, even as may be HMC synthesis in normal cells.

In the course of our efforts to understand the behavior of the thymine-requiring bacterium, several phenomena were found (11) which I feel are of the greatest interest to cell pathologists. Thymine is specifically a nuclear constituent. In the absence of exogenous thymine, cytoplasmic synthesis continued, resulting in the doubling of the ribose nucleic acid with a concomitant increase in proteins and enzymes. In the absence of DNA synthesis the cell can even make a new enzyme in response to a suitable inducing substance.

Cells produced under these conditions become enlarged and swollen, and after a brief lag without increase in viable count, then irreversibly lose the power to multiply. In effect, they "die" at the rate of 90% per division, if death can be considered to be the loss of the power to multiply. Death in this sense occurs only as a function of the utilization of glucose, nitrogen and phosphorus. The cells must synthesize and grow in order to die. The loss of the ability to multiply occurs when the growing cytoplasm provides a structural framework in which the nucleus can no longer divide; the cell dies as a result of unbalanced growth.

We have found that death can be induced in other bacteria by producing a thymine deficiency under conditions suitable for cytoplasmic growth. Further we have shown that ultraviolet irradiation kills irreversibly under conditions in which metabolism and synthesis are permitted. This occurs at the same rate as thymineless death and results in the same cytological picture.

It appears that a number of other important killing agents such as the nitrogen mustards, certain antibiotics, and Amethopterin may function in the same manner. They induce death in bacteria by inhibiting DNA synthesis with very slight effects on cytoplasmic synthesis, i.e., they cause unbalanced growth. It would seem that all of these agents can be grouped together with ultraviolet irradiation, and with thymine deficiency. It seems quite reasonable to me that these agents should then be effective in the inhibition and therapy of pathological growth, and a recognition of their common effects should permit the improved design of such agents.

The study of pathology has long been one of the most fruitful approaches to normal metabolism. Our devious path of research which started with T2 infection, and continued through thymineless death and unbalanced growth, has most recently led us to another type of phenomenon which should be of

considerable assistance in clarifying problems of both normal development and of cellular pathology.

If the thymineless mutant is held without thymine for too long an interval it will die. If thymine is added to the medium shortly before death begins, a startling development occurs. The cells do not die nor do they divide for approximately thirty minutes. They then all divide together, stop together, and are now almost completely synchronized in subsequent divisions.

If nucleic acid synthesis is followed simultaneously, it is found that DNA synthesis begins shortly after addition of the thymine and parallels the synchrony of division, preceding it by some minutes. Thus DNA synthesis precedes division and stops during the actual division. This process in bacteria is then exactly comparable to the doubling of DNA in interphase observed in higher cells and to the absence of DNA synthesis occurring in mitosis proper. Higher cells are not readily subject to experimentation however, since higher cells are not readily obtainable in the synchronized state. On the other hand, our bacteria are very easy to obtain in this condition and we can begin to study such phenomena as virus or antibiotic susceptibility as a function of the stage of cell division as well as the relation of a wide variety of metabolic events to the life cycle of the cell.

As a result of my experiences with the T-even phages and several strains of *E. coli*, I have been impressed by the differences between these biological systems and others described in the literature. In the last few years it has been elaborately established that viruses, hosts, and infected cells may vary considerably in their composition, properties, and patterns of multiplication. There can be no doubt that the differences in composition between T2 with HMC and T3 with cytosine are real and important, as are the differences between a phage or vaccinia with DNA, and a plant virus with RNA. The release mechanisms of a bacterial virus and influenza virus are markedly different and it would be unwise not to look for characteristic differences in the details of their adsorption and multiplication as well. Thus extrapolation from T2 and *E. coli* to human pathology is evidently a dangerous jump. Nevertheless the work with our model system has already borne fruit in the design of experimentation in animal virology and it may be anticipated that advances in this field will multiply as a result of the basic information obtained from the lowly bacteria and bacterial viruses.

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S. Weir Mitchell, the Neurologist*

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It is a great pleasure for me to speak on this memorial occasion of a pioneer in American medicine who wrote his name so large in the annals of neurology. I regard it as a special honor to have been invited to make this address in the city in which the man whom we are memorializing lived and worked and on which he shed so much luster. But I also have a sense of inadequacy for the task and not a little trepidation. Here I stand in Philadelphia before a group of eminent neurologists and psychiatrists, some of whom may still recollect the great doctor, the city which with considerable justice and no undue exaggeration may be regarded as the cradle of American neurology if not also the first center of medicine. Here lived and worked many pioneers, to mention without invidious comparison only a few, who contributed to the growth of neurology, among them Charles K. Mills, in my opinion one of the most outstanding of American neurologists, William G. Spiller, Charles W. Burr, Charles S. Potts, Williams B. Cadwalader, Francis X. Dercum, Charles H. Frazier, Theodore H. Weisenburg. And so it becomes a little presumptuous on my part to record, what has been better and more learnedly told by others, the life and the contributions of the subject of this address. And yet I am grateful for this opportunity to retell the story of one of our noted forbears in neurology and to draw some inspiration and perhaps a few parallels from the creative life of a doctor, a scientist, a poet and novelist and, what appeals to me most strongly, a humanist.

* Read at a joint meeting, 5 November 1954, of the College of Physicians of Philadelphia, Section on Medical History, and the Philadelphia Neurological Society, commemorating the 125th anniversary of the birth of S. Weir Mitchell.

Though the topic assigned to me by your president is S. Weir Mitchell, the neurologist, may I be permitted to digress for a moment to speak of him first as the cultured doctor, the humanist physician. It has always seemed to me that the great neurologist, like other great doctors, should be a little more than a specialist in his own field. Clearly the neurologist must be complete master of clinical neurology and have thorough grounding in neuroanatomy, neurophysiology and neuropathology. He should have sound acquaintance with internal medicine and possess deep insight into psychiatric states. One simply cannot be a well-rounded clinical neurologist unless one is also a good psychiatrist, and it is not possible to practice the one without knowledge of the other. Whereas many psychiatrists, much to the detriment of progress, I believe, appear to have little interest in the structure and function of the brain, the practising neurologist does not share this major disdain or the cavalier approach. The eminent neurologist should also be a scholarly doctor with genuine love of literature, including the great classics of all times, and have a live interest in general history. Without an historical perspective, it may be added, there can be no culture at all. If, in addition, the neurologist be a man of wisdom and understanding with warm insight into human foibles and human folly and possesses the sense of humor which enables a man to laugh at himself, the desiderata for eminence are possible of fulfillment. As an aside, I have always held to the view that a genuine sense of humor is a better index of intelligence, if not also of character and personality, than some of the current psychometric tests.

That noble breed of philosopher-poet-belle-lettrist-humanist-physician of days gone by

has unfortunately and regrettably, though inevitably, almost disappeared. When learning took the place of knowledge and when knowledge itself was quite scant many a scholar could take all of it for his domain. Roger Bacon did and so did Erasmus, who also knew how to praise folly. As knowledge accumulated it grew so vast that it became more and more difficult for one single mind to encompass all of it. What with the tremendous development of science it is now almost impossible for one who would be master in his own field to pasture in neighboring fields. Almost but, I hope, not quite. Rabelais is adduced as an outstanding example but, truth to tell, he was not a great doctor. Aside from his translation of the aphorisms of Hippocrates from Greek into Latin he contributed nothing to medicine. His fame rests on his creation of Pantagruel and Gargantua and on his wit and humor. The fame of Sir Thomas Browne derives from his "Religio Medici" and his discourse on "Urn Burial," and he too is not known for his achievements in medicine. Many physicians became famous as literary men only after they deserted medicine. Arthur Schnitzler grew to fame as a dramatist; Anton Chekhov as both novelist and dramatist; Conan Doyle challenged Poe and Gaboriau with his detective stories; Somerset Maugham wrote "Of Human Bondage," a great novel, and Cronin practised medicine for a time but left it to become a novelist. Sir Ronald Ross, who discovered the mosquito which carries the malaria plasmodium, wrote poems and novels and dramas, composed musical pieces and even put his hand to sculpture and painting. In this country Oliver Wendell Holmes attained fame during his lifetime in both fields, but without aspersing his genuine merits it may be said, perhaps sotto voce, that he did not attain eminence in either. S. Weir Mitchell alone did in both. While his poetry, with the exception of his "Ode on a Lycian Tomb," has largely retired to honorable, if a little dusty, shelves, some of his novels can still be read with pleasure and profit. In the history of neurology his name is forever meritoriously inscribed.

Though much has been affectionately written about the life and creative achievements of Doctor Weir Mitchell, as he loved to be called, it is appropriate to recall, however briefly, why we are here to honor his memory. We of this generation may still learn instructively from first hand study of the great contributions of the pioneers in our field who in little more than two generations built the house of neurology in which we now live. One occasionally observes a tendency to derogate somewhat superciliously doctors of old as not modern, and so it is well to recall to failing memory the truism that not everything that is modern and recent is a contribution and not all great contributions are either modern or recent. It is good for every craftsman to know the history of his craft, and very good in that it conduces to beneficial modesty. A scholar's reward awaits those who would browse in the books and articles which came from Mitchell's pen. For me it was a great pleasure to do so in preparation of this somewhat rambling discourse.

S. Weir Mitchell, as many of you know, was born on February 15, 1829. His grandfather, Alexander Mitchell, was a practitioner of medicine and his father, John Kearsley Mitchell, a good doctor who taught medicine at Jefferson Medical College, loved learning, and is reputed to have been a modest poet in his own right. Young Weir's early life and adolescence were uneventful, seemingly without evidence of special gifts to portend a brilliant future. However he did become an avid reader and apparently acquired a taste for history. Before entering Jefferson in 1848 he attended some of his father's lectures. After two years of study he was graduated in 1850. With few honorable exceptions medical teaching in America was at a fairly low ebb and opportunities for advanced research such as existed in England and Scotland and especially in France and Germany were entirely wanting. And so young Doctor Mitchell went to Paris where he learned microscopy, spent

about a year in Claude Bernard's laboratory, and came home with a microscope. On his return he set out to practice medicine in his father's office.

The first paper he wrote was on uric acid crystals. He soon became interested in vegetable poisons and snake venom, which led to the investigation of its alkaloids. His physiological and toxicological interest in the subject continued with interruptions for more than fifty years. As early as 1860 the Smithsonian Institution published a 150 page treatise on snake poisons. As late as 1901 he gave Noguchi a fellowship for the study of venom and so put the Japanese scientist on the road to fame. Twenty-five years after the beginning of his researches Mitchell collaborated with Reichert on the action of venoms.

It was in 1862, when Mitchell became a contract surgeon in the U. S. Army and took up his studies on soldiers wounded in the war, that his neurological career began. Surgeon General Hammond set up in Turner's Lane a 400 bed hospital for nervous diseases and nerve wounds. There Mitchell collaborated with G. R. Morehouse and W. W. Keen, having made the acquaintance of the latter in 1860. While his main studies dealt with nerve injuries he was interested in the epilepsies and in chorea, especially post-chorea paralysis. As early as 1864 he wrote with his two collaborators, "Gunshot Wounds and Other Injuries of Nerves," wherein he described the syndrome of causalgia, ascending neuritis, and stump palsies. He also described reflex paralysis from remote wounds, a subject which Tinel, who was familiar with the French translation of Mitchell's book, studied during the first World War. The good doctor originally described erythromelalgia which for a long time was known as Mitchell's disease. Nor did he fail to observe psychic phenomena in soldiers with nerve injuries and otherwise wounded soldiers. He even distinguished between hysteria, cowardice and malingering.

His interest in neurology having been awakened during those early years he pursued with zeal and industry the studies which found expression in innumerable important contributions. In 1869 he published a resumé of his studies on the cerebellum. These were based on animal experiments, pigeons, rabbits and guinea pigs, the investigations dealing with ablations, freezing, irritation with cantharides, and penetrating wounds. He thought that the cerebellum was an organ reinforcing the spinal cord, an error to be sure but not too violent a one. From 1870 to 1879 he published thirty-nine papers and three books on neurology. In 1879 he became physician to the Orthopedic Hospital, which was to include later the name of Infirmary for Nervous Diseases. It was then that he gave up general practice. Charles K. Mills became his protégé and in 1877 he helped his younger colleague to start a department of nervous diseases at Blockley. Mitchell wrote on neuralgia in locomotor ataxia, pain and weather, headache and eyestrain, facial tic, spastic paralysis, and the knee and ankle jerk. He not only studied the various forms of neuritis but the causalgia, already alluded to, both as a symptom and a syndrome, the trophic disorders, and the physical and mental manifestations the result of amputation of limbs. He investigated minutely the cutaneous supply of nerves and noticed that the area of cutaneous loss did not correspond to the anatomical distribution, in which he recognized overlapping, and so was a forerunner of Henry Head. He employed massage and electricity in the treatment of nerve injuries, advocated nerve section and nerve stretching and ice and sprays for the relief of local spasm and the reduction of pain.

The contribution which brought the good doctor his greatest fame as also his severest criticism was his Rest Cure, better known as the Weir Mitchell Treatment. Though he first described it at some length in 1873 in the *American Journal of the Medical Sciences*, he continued to contribute articles and books on the subject almost to the end of his days. He even embodied his pet theme in some of his novels. Critics not always animated by admiration and regard or honestly outraged

by an affront to literary or scientific truth pounced on Mitchell unmercifully and held him up to ridicule. His books on "Fat and Blood," "Wear and Tear" and "Lectures on Diseases of the Nervous System, Especially in Women" lent themselves particularly well to their hostile arrows, the points sometimes dipped in literary venom, and aimed with unconcealed glee. He was ironically called a fashionable doctor and actually stigmatized as a charlatan. But one may observe in passing that the avidity with which some critics attack gifted men with original ideas is not always motivated by scientific ardor or passion for truth. To which may be added the observation that critics can be and often are more sensational than authors and that some indulge a human failing in the vain belief that they can increase their own stature by cutting down that of others.

It is true that the Rest Cure has lost much of its reputation as time marched on, but it is equally true that the kernel of truth which it embodied is still bearing fruit. Conceding that the theory underlying the treatment has lost its validity in the face of advancing knowledge, it will serve a more useful purpose to stress the very genuine contribution which Mitchell did make. Without intended offense it may be said that much of what passes for science in modern psychiatry will probably turn out to be no science at all, and it needs no prophet or the son of a prophet to predict that what is now pontifically acclaimed as profound psychology may turn out to be plain gibberish and become the butt of future critics. All of which, perhaps as a non sequitur, does not prevent people from writing volumes about things which can better be said in paragraphs; and it merely confirms the dictum of Ecclesiastes that of the making of books there is no end.

The very important contribution of Mitchell was his insight, though not quite so explicitly stated, into the role of the emotions in illness in general and in the neuroses in particular. The evidence of his recognition of the importance of psychic factors in disease consisted in his efforts to influence the minds of his patients. Charcot, the father of modern psychopathology, gave expression to the idea by means of hypnosis and suggestion, Binswanger too stressed the importance of the emotions, and George Beard, in this country, coined the word neurasthenia in 1869. Mitchell, it may be recalled, also wrote on dual personality. This profound insight into human motivation, which incidentally finds expression in what may be called his psychiatric novels — "Constance Trescot," "In War Times," "Characteristics," and "Dr. North and His Friends"—almost marks him, without offense to his memory, as a psychoanalyst or at least as a therapist with analytic insight into human behavior. He had no knowledge, of course, of the libido, of orificial erotic complexes or of the edipus situation; but it may be asserted, I believe, without grave fear of contradiction that Sophocles too did not set out to write a sex drama when he composed "Oedipus Rex" and Shakespeare did not know that when he created "Hamlet" he designed to give literary proof of the existence of the edipus complex.

Lest these few remarks convey the erroneous impression of hostile criticism may I say that not only am I not unfriendly to analysis but that I yield to nobody in my appreciation of the great contributions of Freud and my regard for the profound insight into unconscious human motivation which he vouchsafed. But one need not, indeed must not, abdicate reason when dealing with medicine as a science, nor in practising the psychiatric art become the slave of a tool instead of its master. A great deal of what Freud said can be rejected with good reason, and one can only do grave injustice to his original contributions of permanent value by swallowing whole and uncritically much that is scientifically indigestible. One must ever beware of seductive language and constantly remember that palatable literary composition and even beautiful writing can conceal some very bad thinking.

There is one other field in which Mitchell may with permissible interpretation be

credited with some pioneering insight. I refer to the word psychosomatic, a confusing shibboleth which in its true meaning merely represents a point of view and not a medical specialty, certainly not a medical science. It is quite clear that our good doctor was not aware of the theory underlying what now euphemistically passes for psychosomatic medicine and could not formulate it in modern terms, but he practised it just the same even as people in ordinary conversation often use a metonymy or synecdoche without being aware of the fact or knowing how to define either word. Without deprecating the subject, because there is in it a kernel of truth capable of bringing forth valuable fruit, one may more than diffidently call attention to the frothy shell which envelops the kernel. Unfortunately it is a common human failing to mistake theory for fact and to bridge with words gaps in knowledge which science cannot fill. There is also the quaint notion, somewhat akin to a minor delusion, that to coin a word is to create a fact. With apology to sensitive souls, this is neither good medicine nor good science.

If the exponents of psychosomatics are sometimes questioned Socratically to define the word or are merely asked, How do you know?, they are somewhat hard put to it to tell what it means. The fact is that the word is merely a modern formulation of the old body-mind idea which has been scholastically debated by doctors and philosophers and theologians for centuries if not millennia. When the ancient Greeks coined the word hysteria to explain the emotional havoc ostensibly caused by the peregrinations of the womb, or melancholia to indicate the psychosis caused by black bile, or hypochondria to show how something below the cartilages gives rise to a somatic delusion, they spoke in psychosomatic terms. They erred obviously, as we often err today, but the concept was there none the less. What is important in the modern formulation is the observation that bodily disease can cause mental and emotional disturbances and that continued anxieties, tensions, frustrations and conflicts can ultimately express themselves in bodily disease. Assuming the correctness of the theoretical formulation its truth is not established by endless reiteration of the theory or repetitious presentation of unconvincing case reports. What the neurologist, who is convinced that there can be neither function without structure nor structure without function, wants to know is how does the disturbance come about and what structures are involved. What are the physiological or biochemical processes, what have the brain, the hypothalamus, the ascending and activating reticular system, the vegetative nervous system, the endocrines to do with the reciprocal reactions labelled psychosomatic? Until science provides the answer the psychosomatic point of view will continue to express an old idea or a modern theoretical concept, a hopeful one to be sure, but still only an idea. Weir Mitchell, I think, had the idea.

It is conceded that in addition to being an active clinician Mitchell was also a good scientist, but it may be well to inquire, in view of the loose way in which the word scientist is frequently used, what characterizes the scientist. To be a true scientist one must possess absolute intellectual integrity, unquenchable curiosity, the capacity for objective criticism, courage to maintain and defend one's views, obsessive persistence in the pursuit of problems, and almost demonic ability to work. The last has been defined as the infinite capacity to take pains. However, important as all these characteristics are, what makes a truly great scientist, as it does all men of genius, is the gift to see new relationships. This alone makes for originality. While many do scientific work and often make valuable contributions few are endowed with imagination, with the poetic spark or the ability to dream, all so necessary to discover relations previously unsuspected. One may conclude that, whether or not Mitchell was a great scientist or a man of genius, he possessed in good measure some of the qualities of both.

Weir Mitchell was not a cloistered scholar but he loved learning and he loved books. Early in his medical career he came to know

Billings who, as you know, laid the foundation for the growth of the Surgeon General's Library and initiated the *Index Medicus*. Like Osler Mitchell showed interest in medical history and he searched out first editions and rare medical books for the library of the College of Physicians of Philadelphia. In 1891 he gave an address on "The History of Instrumental Precision in Medicine." Love of learning, in my opinion, is greater than learning. With all due respect for scholarship, some who are only scholars, in that they know everything others have said without saying anything original themselves, occasionally show pride akin to arrogance; which is only a little less distressing than the arrogance born of ignorance. Love of learning begets admiration which in turn begets modesty.

Despite the fact that both Jefferson and the University of Pennsylvania rejected him early in his career when he was a candidate for a professorship, Mitchell was a teacher. Mills, Cadwalader, Throckmorton, Beverly Tucker and Noguchi were really his pupils. While Pepper and Osler, and more Pepper than Osler who soon left for Hopkins, are credited with making the University of Pennsylvania Medical School a great center Mitchell contributed in many ways to its growth. He had great capacity for friendship and he counted among his friends Pepper, Billings, Osler, Welch, Holmes, William James, and many others. Being a Philadelphia aristocrat of Virginian lineage who knew how to eat cherries with pits at formal dinners, he advised that the young Canadian doctor whom he recommended for the professorship in medicine be subjected to the test of polite eating. Fortunately Osler passed the test with credit to himself and no disgrace to Mitchell. Think what American medicine owes to a cherry pit.

It would take too long to enumerate the many honors, including honorary degrees, which came to Mitchell. When the American Neurological Association was organized in 1875 he was elected the first president but he declined to serve. Curiously, it was not till 1909 that he became president of the Association. In 1884 he was elected president of the Philadelphia Neurological Society. Jefferson, as if to atone for its failure to accept him as professor many years before, conferred an honorary degree on him when he was eighty-one years of age, and what can one do with an LL.D. at eighty-one? His long productive and creative life came to an end on January 5, 1914 just six weeks before he reached the venerable age of eighty-five.

And so we come in brief outline to the end of our story of S. Weir Mitchell, the neurologist. When he became a doctor in 1850 medicine was in a low state and neurology, with honorable exceptions, James Jackson being one of them, was practically without status as a discipline. Scientific neurology according to Neuburger only began in 1820 with Bell and Magendie. Romberg wrote the first comprehensive textbook of neurology in 1846. Clinical neurology was the stepchild of medicine and a neglected urchin in psychiatry. It actually began with Duchenne de Boulogne and Broca and Charcot, with Erb and Westphall, who in 1875 became the first professor of neurology in a German university, and Jackson and Gowers, and a host of other men of eminence. They described and classified the clinical entities as we know them today and brought order out of clinical confusion. Mitchell belonged to that galaxy of neurologists. Many American neurologists of eminence followed him as American medicine came of age, but it was he who truly pioneered in this country. Combining in himself, as he did, the poet, the novelist, the doctor, the neurologist and psychiatrist, he was in the true tradition of the humanist, a man of unique stature. What more can contemporaries demand or posterity record?

S. Weir Mitchell as Man of Letters*

By ERNEST EARNEST, PH.D.

Professor of English, Temple University, Philadelphia, Pa.

I CAN think of no more fitting place than this for a meeting in honor of Dr. S. Weir Mitchell. The College of Physicians was always dear to his heart; in fact the choice of this location was in considerable measure due to Mitchell, and his diaries are filled with references to fund raising for this building. These same diaries give more than a suggestion that the sometimes opinionated doctor did a good bit of wire pulling and politicking—and at times bulldozing to bring about the move to Twenty-Second Street. In 1904 he noted in his diary: "200 M.D.'s decided by 96–62 to move to 22 st. . . . the Pa. Hosp. men were as usual stay still folk. There is a local infection there of unenterprize . . . great election work."

In particular the library of this organization was his special interest. His letters to Dr. Osler and to other friends interested in the history of medicine contain frequent references to rare volumes Mitchell was in search of for this library. One night when Mitchell was in search of some book in the stacks here, the lights went out. He got a candle from the janitor, but this too went out. Suddenly he felt himself in a vast burial place where eight thousand books were "tombs with inscriptive titles to which the living years continually give the lie." A sense of the immense vanity and futility of all this effort came over him. Then his mood changed. Here was a record of a vast army forever winning or losing, forever recruited. What books would one ask for after 200 years? His answer was prophetic: "In that day a professor will say to his class it is needless to tell of yellow fever or plague because there are no such maladies now. Then shall cancer be a defeated foe, and tubercule a lightly regarded disorder, and typhoid a curio of hospital records." (1909)

That was written by a man who understood the use of books: books not only as tools for research, nor old volumes merely as decorations for a collector's shelves. For Mitchell books were a stimulant to the imagination. He once jokingly told some students that his reason for writing novels was that he had read all there were worth reading, and therefore decided to write some of his own.

I am glad that Dr. Padis suggested as the title of this talk, "Dr. S. Weir Mitchell as Man of Letters." That gives me an opportunity to speak of something larger than Weir Mitchell as Novelist and Poet. For there is no denying the fact that Mitchell is not one of the great figures in American Literature. In his own day he suffered from overpraise: *Hugh Wynne* was compared to *Henry Esmond*; the *Ode on a Lycian Tomb* to *Lycidas*; in our day he is undervalued, except perhaps by some Philadelphians who regard New York writers as upstarts and who believe Paoli to be the western boundary of civilization.

It seems to me that it does no service to Dr. Mitchell's memory to try to picture him as a great author. Perhaps Walt Whitman put his finger on the main point when he remarked: "I can't say that he's a world-author—he don't hit me for that size—but he's a world-doctor for me—leastwise everybody says so and I join in."

Mitchell always regarded himself as primarily a physician, only secondarily an author. Or at least he kept this perspective except when after-dinner speakers hailed him as a Thackeray or a Milton. Following one such occasion Mitchell bemoaned the fact that he could not

* Read at a joint meeting, 5 November 1954, of the College of Physicians of Philadelphia, Section on Medical History, and the Philadelphia Neurological Society, commemorating the 125th anniversary of the birth of S. Weir Mitchell.

get Charles Eliot Norton to repeat in print his banquet-speech estimate of Mitchell's verse.

At the risk of raising the hackles of professional Philadelphians I must report that Mitchell's poetry is pretty undistinguished. That is not entirely his fault. He wrote in a period when such people as Richard Watson Gilder, Edmund Clarence Stedman, and Thomas Bailey Aldrich were accepted by literary magazines which rejected Walt Whitman and Emily Dickinson. It was men like Gilder, Stedman and Aldrich who as writers and editors dictated American taste. Mitchell himself, although he helped to support Whitman, described him as a poetic tramp. Had Mitchell been a really good poet he couldn't have got his work published in 19th century America. And I fear that a good poet could not have enjoyed his fashionable Philadelphia medical practice.

As a novelist Mitchell stands up better. I would like to see some of his novels reprinted—not because they are hard to obtain, at least at Leary's, but because modern readers tend to refuse to read anything printed before 1950. To be read today a good older work must come out with a sexy dust jacket or in a plastic backed edition showing a lusty wench in a low-cut gown.

Perhaps *Hugh Wynne* could do all right if it came out with a picture of the heroine Darthea Peniston in a ball gown and with the blurb: "Would this beautiful Philadelphia belle choose her Quaker lover or his handsome aristocratic British cousin? A dramatic novel of the conflicting loyalties of the Revolution set amid the glitter of Philadelphia's most glamorous social season."

Ironically enough, this blurb would not do too much injustice to the book. *Hugh Wynne*, the best selling novel of 1896, is essentially pretty phony. The characters, the plot are all borrowed from countless historical romances. What gives it some vitality is Mitchell's thorough knowledge of history: he knew what people ate, wore and talked about. It has a lot of glamorized historical information. Therefore it's a book which has appealed to school teachers. For over 50 years it has been on high-school reading lists.

It is far from Mitchell's most important novel. Beginning in 1880 he published about 14 volumes of fiction. The first volume is made up of short stories and a novelette. But to a man of my age it is most encouraging to note that his first real novel came in 1884 when Mitchell was 55 years old. I might add that he was 67 when he published his best seller *Hugh Wynne*, and 76 when his best novel, *Constance Trescot* appeared.

It would be impossible, as well as highly boring, in a talk such as this to analyze in detail Mitchell's work as a novelist. To me his most significant quality is his knowledge of people as seen by a pioneer psychiatrist. In the typical Mitchell novel there are two types of characters: the well-portrayed stereotypes such as the fascinating woman and the brave hero, and secondly the case histories. But Mitchell is a good enough novelist to make his case histories into real people.

There is Dr. Ezra Wendell in the first novel, *In War Time*. A weak man, but with sensitivity and imagination. I suspect that in portraying Dr. Wendell, Mitchell exorcised some of his own personal devils when for instance he remarks after Dr. Wendell has lost a patient, "There is probably no physician who cannot recall some moment in his life when he looked with doubt and trouble of mind on the face of death."

There are other well-drawn characters: Wendell's righteous, unimaginative sister, who runs his household efficiently, but who torments him with her ritualistic tidyings-up. There is Mrs. Grace, the busybody, who is a fearful nuisance to the other ladies working for the Sanitary Commission in the Civil War, and Mr. Grace, "who believed in The Pennsylvania Railroad." In Mrs. Grace, Mitchell has drawn what I should guess is the bugbear of every physician: "the woman who runs from doctor to doctor in search of one who shares her prejudices."

I realize that it would be highly confusing to

pick a score of characters from a dozen or so novels. Therefore I shall mention only a few. In his second full-length novel, *Roland Blake*, Mitchell presented an unusual study of a neurotic woman, Octopia Darnell. She is one of those demanding semi-invalids whom Mitchell had described in his medical book for laymen, *Fat and Blood*. Her fondness for physical petting repels her young cousin Olivia. Octopia's emotional vampirism has its effect on Olivia, whose state Mitchell describes with Freudian insight: "Her head ached, and with the consciousness of constant fatigue, the outcome of a life of strain and repression, began to come its certain result, irritability." The homosexual implication in Octopia's feeling for her cousin is of course carefully veiled, but it is there. Mitchell speaks of the unhealthiness of the relationship, and vividly portrays Olivia's physical repulsion.

Then there is the Rev. Cyril Knellwood in *Circumstance*. "Underfed and overworked" he was "just in the condition when emotions are apt to get out of control." The Rev. Mr. Knellwood, who had vowed himself to celibacy is dangerously attracted by the "beautiful half-trained animal," Kitty Fairthorne. Kitty is described thus: "as nearly an instinctive creature as evolutionary forces and educational training permit a young woman to be." Not only is the repressed Knellwood attracted to Kitty, he also declares war horrible but loves the battle line.

In the same novel is the wealthy business man, Roger Grace, also sexually repressed, who goes off on periodic binges. Here is no ten-nights-in-a-barroom caricature; Grace is a sensitive, brilliant man turned alcoholic through psychological mal-adjustment.

Characters as psychologically complex and so well understood as Dr. Wendell, Octopia Darnell, the Rev. Cyril Knellwood, and Roger Grace are rarely drawn by nineteenth century American novelists except the very best: Hawthorne, Melville, and Henry James.

In a number of Mitchell's other novels there are interesting psychological studies, but perhaps the most interesting is that of Constance Trescot in the novel by that name. As I have mentioned, Mitchell published it at the age of 76. It is the story of a possessive wife who avenges her husband's murder. She is described as "one of the rare women who, for good or ill, attract because of some inexplicable quality of sex. Incapable of analysis, it accounts for divorces, ruined households, even for suicide or murder. It may be faithful to a great passion, and be modified by character or education, and even by religion, but it is felt, whether the woman wishes it or not, and she who has it instinctively knows its power."

Not many English speaking novelists in 1906 spoke so openly of sex appeal.

Even at 84 Mitchell produced an interesting novel, *Westways*. Fearing that he might die before it was published, he jumped on a train for New York with the manuscript, and importuned his publishers to bring it out at once. It too contains an interesting case history, the study of the decay of a fine man due to a head wound which affects his mind.

Then too there are vivid pictures of the Battle of Gettysburg. Mitchell tells of "the strange and complex odor which rises from a battlefield," of the screams of wounded horses, of a baker's wagon wiped out by a shell, of the army post office marking letters " 'not found'—'missing' and so on." War is described thus: "A disgustingly dirty business. You don't realize that in history, in fiction, in pictures. It's filthy." In fact as far back as 1884 with the novel *In War Time* Mitchell had anticipated Stephen Crane and Hemingway in his pictures of war without glamor. And in *Roland Blake* there are vividly realistic scenes: the dull thud of bullets hitting trees and "duller sound on limb or trunk of man." Waiting for an attack one man incessantly wipes his gun-barrel, another buttons and unbuttons his coat. We see men shot, stabbed, beaten down by clubbed muskets, and there are ghastly pictures of a battlefield after a charge.

One thing I noted in going through notebooks Mitchell kept late in life: he was consciously trying to add a new dimension to

his writings. He was training himself to note sense impressions, the colors and forms of shadows in a trout stream, for instance. It is therefore no accident that his later novels are as vivid in detail as those of 20 or 30 years earlier.

I wish I had time to talk about Mitchell's conversation novels, *Characteristics* and *Dr. North and His Friends*, novels filled with talk by intelligent people about interesting and provocative ideas. And I have no time to discuss his children's stories or his short tales of mystery and adventure.

But I want to speak briefly about Mitchell as a writer on medicine. In the library of the College of Physicians there are about 80 of Mitchell's case histories of patients at the Turner's Lane Hospital. This was a Civil War hospital to which men with neurological ailments were sent, and where Mitchell, Morehouse, and Keen did brilliant pioneering work. Now I am not a physician, but I found these case histories so clearly written in nontechnical language that they were completely clear to a layman.

For instance here is a passage from his first published story, in which he explains why a patient feels pain in an amputated limb: "the nerve is like a bellwire. You may pull it at any part of its course, and thus ring the bell as if you pulled it at the end of the wire; but in any case, the intelligent servant will refer the pull to the front door, and obey it accordingly."

To me one of Mitchell's most interesting medical writings is *Doctor and Patient*, 1888. It is essentially a series of lay sermons, most of them addressed chiefly to women. In it he put a wealth of illustrative anecdote drawn from his medical practice. The introduction contains a remarkable paragraph on the treatment of neurotics, a paragraph pointing out the need for the physician to let the patient pour out confessions of a whole life. For says Mitchell, "The causes of breakdowns and nervous disaster are often to be sought in the remote past." Let me repeat the date of that—1888.

The opening essay in *Doctor and Patient* is titled "The Physician." In it Mitchell charmingly combines his knowledge of medical history and his experience as physician and psychiatrist.

Mitchell had an enduring interest in medical history. Dr. Logan Clendening searching for material on the subject found Mitchell's little book *The History of Instrumental Precision in Medicine* the best treatise on that topic. But perhaps the versatility of the man is best illustrated by Dr. Harvey Cushing's account. After a medical meeting young Dr. Cushing was invited to what he described as "a memorable midnight session" in Mitchell's study:

> It was a capacious room dominated by two portraits—copies of the Reynolds' Hunter and Janssen's Harvey . . . I remember his pointing out how clearly J. had portrayed Harvey's arthritic knuckles. Then there was a beautiful colored bust of Dante, Keats' death mask, and in a glass case the head, recumbent, of a Roman, as I learned, who had been killed in battle some eons ago outside the walls of Ravenna. M. said it was of Guidarello Guidarelli . . . "Jack", he said, "I once wrote some verses on Guidarelli." Whereupon Jack got out a volume of his father's poems from the shelves which lined the wall and read the verses aloud . . . He subsequently gave me a copy of the book . . . adding that the publishers had never been able to dispose of them . . .
>
> There was much more about books after this and I recall Rob't Burns' copy of Pope, a presentation copy of Robinson Crusoe; and something brought up Mrs. Piozzi, whereupon Jack got down a copy of her Johnson . . . The copy I think had belonged to Horace Walpole & later to Thackeray . . .
>
> We must have lingered on from about eleven to three A.M., Dr. M. meanwhile smoking a succession of heavy cigars and he finally got out some old Madeira with a history of three times around the Horn.

To me that brings back an era when successful men also prided themselves on their knowledge of books. Today, at least in my profession of teaching, we are specialists, technicians. Weir Mitchell was a humanist, a real man of letters, a man to whom books were an essential part of life. In his old age he helped to found, and was first president of the Franklin Inn Club, a club originally composed largely of authors. Now that Philadelphia no longer has authors, the club is full of newspaper men and college professors.

As a child Mitchell lived in a house where books were passionately discussed at the dining table, and where Edgar Allan Poe and Oliver Wendell Holmes were honored guests. As a mature man he found time in a busy—and I may add, profitable—practice to write a whole shelf of books, everything from medical papers to poems and from children's tales to psychological novels. Oh yes, and I forgot to mention a scholarly life of Washington and the translation in verse of a medieval poem.

And as Dr. Cushing's account makes clear, Mitchell lived among books; he talked about books over cigars and good wine. He studied books, he wrote books; above all he enjoyed books. Weir Mitchell was one of what today is an almost forgotten species, the true man of letters.

William Edmonds Horner, 1793–1853

By ALFRED RIVES SHANDS, JR.[1], M.D.

THE following is from an obituary on the death of Dr. William E. Horner, printed in the *Philadelphia Public Ledger and Transcript* in March 1853:

> The announcement of the death of Dr. Horner cannot fail to make a profound impression upon the many throughout the wide extent of the country who have derived the first notions of their profession from his teachings or who have been relieved of disease by the exercise of his eminent skill. In this community, his loss may well be deemed a public calamity.

What manner of man was this whose death one hundred years ago[2] made a profound impression upon so many and was deemed a public calamity by Philadelphia's leading newspaper of the day? Dr. Horner was distinctly an average man with average intellect who by sheer force of will rose to the topmost rung of the ladder of success in medicine. He was short, of frail stature with sharp features, never weighing over 120 pounds, born of good Southern parentage on June 6, 1793, in Warrenton, Virginia. As a boy, he was more interested in reading than in outdoor sports. When he was 11 years old his formal education began in Warrenton in the school of an Episcopal clergyman, the Reverend Charles O'Neill and was continued in this same school when it was moved to Dumfries, Virginia. In 1809, at the age of 16 the study of medicine was commenced in the office of Dr. John Spence, a learned Scotch physician of Dumfries, with whom he remained for three years. However, during this time, he attended medical classes at the University of Pennsylvania for two sessions. The War of 1812 began at the time he formally entered the University and with a true sense of loyalty to his country, he applied for service in the medical corps of the United States Army. On July 3, 1813, he was appointed a surgeon's mate and was sent to the Canadian frontier. In this same fall he was given six months leave from the Army to complete his medical education at the University of Pennsylvania and was graduated on April 9, 1814. Following graduation, the young doctor returned to the Canadian frontier. For a short period during his army career, Dr. Horner was placed in charge of a hospital. From his own description of his military service in the *Medical Examiner* of 1852 he undoubtedly had unusual and valuable experiences in military medicine. After being discharged from the Army, he returned to his home in Warrenton where he practiced for a few months, but soon appreciated that his ambitions could never be realized as a practitioner in a small Virginia town.

On December 3, 1815, Dr. Horner arrived in Philadelphia, an unknown young man of 22 years with few friends and little money, but with an indomitable spirit and an ambition to succeed. Success came to him gradually over the next 38 years until at his death, Dr. Horner was considered by many to be Philadelphia's foremost physician. His life and accomplishments can be more readily appreciated with the following grouping of his career:

1. Horner, the Anatomist
2. Horner, the Pathologist
3. Horner, the Surgeon and Practicing Physician

[1] Visiting Professor of Orthopaedic Surgery, University of Pennsylvania School of Medicine; Medical Director, Nemours Foundation and Alfred I. du Pont Institute, Wilmington, Del.

[2] This paper, by a Fellow of the College who is a great-grandson of William Edmonds Horner, was prepared in 1953, to commemorate the 100th anniversary of the death of this illustrious Philadelphia physician. Its receipt late in that year, and prior obligations, have prevented its publication closer to the anniversary year. [Ed.]

Dr. William Edmonds Horner
(1793–1853)

4. Horner, the Dean and Administrator
5. Horner, the Teacher
6. Horner, the Man

1. Horner, the Anatomist.

In March, 1816, Dr. Horner's career as an anatomist began. He was appointed a dissector at a salary of $500 a year by Dr. Caspar Wistar who first had recognized his abilities as a student. Soon Dr. Horner gained Dr. Wistar's confidence, esteem, and friendship, but unfortunately two years after this first appointment in the University of Pennsylvania's Department of Anatomy, Dr. Wistar died. This was a great blow to the young anatomist. Dr. Wistar was succeeded, in April, 1818, by the brilliant Dr. John Syng Dorsey, the nephew of the Professor of Surgery, Dr. Philip Syng Physick. Dr. Dorsey immediately advanced Dr. Horner to the position of demonstrator. Following Dr. Dorsey's opening address to his class in the fall of 1818, another great calamity occurred in the Department of Anatomy when he suddenly passed away. Dr. Physick then became the Acting Professor of Anatomy and later, in 1819, the permanent

professor, giving up the chair of surgery, which he had so ably filled for many years. Dr. Physick soon realized the abilities of Dr. Horner and in November 1819 appointed him an adjunct professor which not only was a position of importance and distinction but also carried with it considerable income for that day. During the following years, Dr. Physick's health gradually failed and in 1831 he resigned. After Dr. Physick's resignation Dr. Horner was appointed by the Trustees to be the Professor of Anatomy. So at the age of thirty-eight, Dr. Horner occupied one of the most coveted positions in medicine at the University of Pennsylvania.

The following are the anatomical discoveries accredited to Dr. Horner: 1. The tensor tarsi muscle of the eye was first demonstrated by Dr. Horner in 1824. This muscle is an adjunct to the lachrymal apparatus and was later called the "Musculus Hornerii." 2. The sweat glands in the axilla of the Negro were shown by Dr. Horner to be larger, in greater numbers, and better developed than in the White race, resulting in a more intense odor. Dr. Horner named these glands the "odoriferous glands." 3. Certain peculiarities of the muscular arrangement of the rectum associated with pathological conditions were first demonstrated by Dr. Horner. 4. A fibro-elastic submucous layer lining the inner surface of the larynx was first described by Dr. Horner. This is called the vocal or phonetic membrane of the larynx and is thought most likely to control the tone of the voice. 5. The cartilages of the bronchial subdivisions were first described by Dr. Horner in 1839. He stated that their semilunar form resembles "somewhat the pasteboard of an ear bonnet and is evidently to keep the orifice open."

Dr. Horner was tremendously interested in the Anatomical Museum started by Dr. Wistar. Following Dr. Wistar's death, Mrs. Wistar presented to the University her husband's collection of specimens which Dr. Horner states was the foundation of the beginning of the Museum. From 1820 to 1826, it is said that Dr. Horner brought this Museum from a small collection of specimens to a large one of great interest and importance. In 1831, Dr. Horner speaks of this Museum as being superior in extent to any in the United States at that time. In 1853 following Dr. Horner's death, Dr. Samuel Jackson speaks of the Museum as rivalling the best in Europe. The Museum was originally in a large room which had been the classroom of Professors Rush and Barton. The general plan of the Museum, Dr. Horner states, was that of the Museum of Dr. John Hunter in London. Following Dr. Horner's death the Trustees of the University of Pennsylvania changed the name from the Wistar Museum to the Wistar and Horner Museum because at this time two thirds of the specimens in the museum were preparations of Dr. Horner. This name was used for 41 years until in 1894 General Isaac J. Wistar, a nephew of Dr. Caspar Wistar, presented a sum of money to the Museum for a new building and endowment on the condition that the name be changed back to that of the name of his uncle.

In 1826, Dr. Horner published, under the title, "Treatise on Special and General Anatomy," the first edition of the textbook later called "Special Anatomy and Histology," which had eight editions, the last being published in 1851. This publication soon became the foremost anatomy textbook of the period and had a great deal to do with establishing Dr. Horner's name as a great anatomist. He wrote in 1823 "Lessons in Practical Anatomy for the Use of Dissectors," which book had five editions. The last edition was edited in 1854 by his son-in-law Dr. Henry H. Smith and was called the "United States Dissector." In 1823 Dr. Horner re-edited Wistar's "System of Anatomy." Dr. Horner also supervised the "Anatomical Atlas" published by Dr. Smith.

Dr. Horner undoubtedly was best known as an anatomist. In 1831, when he became Professor of Anatomy, the students of the medical class of that year wrote to him as follows: "We have merely to say that the rank which you hold both in this country and Europe as an anatomist together with your

unanimous election to so responsible and honorable an office speaks language louder and stronger than any we can use."

Dr. Samuel Gross, several decades after Dr. Horner's death, spoke of him as "the most accomplished anatomist that this country has ever produced."

2. Horner, the Pathologist.

Pathology as a specialty in Dr. Horner's early medical career was non-existent. It was usually considered to be a part of anatomy. Dr. Horner, realizing the need for an American textbook on pathology and seeing this as a fundamental weakness in American medicine, met this need in 1829 by writing a "Treatise on Pathological Anatomy." Dr. Horner was not a pathological anatomist. There were no pathological anatomists in that day. However, he had an intense interest in the anatomy of disease, wrote many articles on the subject and lectured frequently on pathological conditions. This first American textbook on pathology had three editions and was the only textbook on the subject for ten years until Dr. Samuel Gross published, in 1839, the "Elements of Pathological Anatomy."

The principal discovery in pathology for which Dr. Horner's biographers give him credit is demonstrating that the rice-water stools of Asiatic cholera are the result of the desquamation of the epithelium of the intestines.

What should be said of Dr. Horner as a pathologist is that he appreciated the need for its teaching, wrote the first textbook on the subject in the United States and did a great deal to awaken interest in this as a special field of medicine.

3. Horner, the Surgeon and Physician.

Dr. Horner's first experiences in surgery were in the War of 1812, as mentioned above. In this war he had an exceptional opportunity for learning the treatment of trauma. He is given credit for first demonstrating the best way to care for a mangled limb which might require amputation; it was described as "an early amputation of just the hanging portion of the leg with the squaring off of the bone ends." This was similar to the so-called "flush" amputation used in World War I.

In Dr. Horner's day, the anatomist also practiced surgery. It was believed that the anatomist with his training in dissection should be skilled in the handling of tissues and should have learned good surgical technique. Dr. Horner not only was an able surgeon but taught clinical surgery in the medical school. Dr. Horner had a large private medical and surgical practice during his whole medical career in Philadelphia.

Dr. Horner is credited, in 1826, with being the first to repair a ruptured Achilles tendon.

Dr. Horner was appointed, in 1823, a surgeon to the Philadelphia Alms House (Blockley), which position he held for 25 years. He was the first Chief Physician and the first President of the Medical Board of the St. Joseph's Catholic Hospital, the third general hospital in Philadelphia in that day. In 1848 he was largely instrumental in the founding of this hospital because of the need for additional hospital beds in Philadelphia for "the better type of patients." He was a member of the Philadelphia Sanitary Board in 1832 and did notable work in the cholera epidemic of that year, having been placed in charge of one of the district hospitals. At the end of the epidemic he was presented by the City of Philadelphia with a large silver pitcher which was inscribed: "To William E. Horner, The City of Philadelphia, grateful for his disinterested and intrepid exertion in a period of public calamity. Transeat in exemplum. August, 1832."

4. Horner, the Dean and Administrator.

In 1822, Horner was chosen Dean of the Medical School. He was then 29 years old. This position he held until 1852. During this 30 year period, largely due to his efforts, great progress was made in the development of medical education at the University of Pennsylvania. It has been said that during his time

never were the finances of the school so well administered.

Dr. Horner constantly strove for better educational standards, which during his latter years the newly organized American Medical Association was constantly insisting upon. During his two trips to Europe in 1821 and 1848, he was greatly impressed with the European system of taking five to seven years in medical preparation before practice. During his day in many communities in the United States, the older doctors were complaining constantly of the numbers of poorly trained young doctors who were being graduated and allowed to practice. Dr. Horner was very anxious that "positive legal enactments on medical qualifications" be established. These never came about in his day but did come not too many years after his death. The College of Physicians and Surgeons in New York and the University of Pennsylvania were apparently the only schools in this day which were trying to raise medical standards. There is no doubt that under Dr. Horner's leadership the highest standards of medical education in the United States were maintained at the University of Pennsylvania.

The following were the requisites for a degree in medicine at the University: 1) 21 years of age; 2) three years study, during which at least two years had to be in association with a practicing physician; 3) one course in clinical instruction in the Pennsylvania or Blockley Hospitals; and 4) an acceptable written thesis.

In addition to being Dean of the Medical School, Dr. Horner was the Dean of the faculty of 1835, which was a great and distinguished faculty and remained intact for approximately 15 years. To be the Dean of the faculty was considered to be a higher honor than to be the Dean of the Medical School. The faculty then consisted of: Nathaniel Chapman, Professor of the Practice of Medicine; William Gibson, Professor of Surgery; Samuel Jackson, Professor of the Institutes of Medicine; George B. Wood, Professor of Materia Medica and Pharmacy; Hugh L. Hodge, Professor of Obstetrics; Robert Hare, Professor of Chemistry; and William E. Horner, Professor of Anatomy. All of these were great names in early Philadelphia medicine.

5. Horner, the Teacher.

Horner was not a brilliant teacher or a fluent speaker. His lectures were straightforward, clear, plain, simple and unadorned. He did not waste words. In fact it is said that he used as few words as were necessary to convey his exact meaning. It is said he made good anatomists of his students and taught entirely by demonstration. He was extremely thorough and tolerated no carelessness on the part of his assistants or students. He always commanded the respect, esteem and affection of all of his students and was extremely popular with his classes.

Dr. Horner often gave advice to his students such as the following: "Let me ask from what sources are we then to look for clear ideas, self-possession, and steady decisive action except information gained and digested in the hours of study."

"With the time appropriated to his practice, to his studies, to his notes, no physician can devote much time to the ordinary pleasures and pursuits of life. He has indeed to exercise a most severe vigilance upon the distribution of his hours to prevent the misapplication of them."

What good advice this is for the young student, and Dr. Horner followed his own advice.

Dr. Horner in addressing a letter to the Student Committee of 1831 who had congratulated him on his appointment as Professor of Anatomy, wrote as follows: "A public teacher ceases to be useful from the moment he ceases to enjoy the confidence of his class." There is no doubt that Dr. Horner always enjoyed the utmost confidence of all of his classes.

6. Horner, the Man.

Dr. Horner's life was a success. As one of his biographers has stated, "His fortune was

a continual flow without an ebb. Nothing he undertook failed. Not a rational wish was ungratified or an aspiration that was not fulfilled."

Nearly everyone who knew him has said that he was not gifted with intellectual powers, but was an average man of average abilities and that he was entirely self-made. It is further stated that "what he was, was wholly his own, the work of rigid self-training and a most labored molding and framing of his principles and character on a high conception of duty in every transaction of life."

He is spoken of as being unassuming, direct in all things, having sedateness and composure of manner, a purity of mind, a strong conscientiousness, and an abiding reverence for whatever he regarded as true, just and sacred.

It has been said that what Dr. Horner did was done as a duty, as an end in itself and never as a means to popularity or fame. He never courted success by a sacrifice of principle to the expediency of the occasion. The love of truth and honor was instinctive with him. He was decided in his own principles of belief and conduct, but he was singularly tolerant of the opinions of others with a tender and delicate regard for their wants and feelings. He was quiet, dignified and sincere. His attitude bred confidence and respect. He was polite, unostentatious and abhorred flattery.

Dr. Horner had deep but quiet religious feelings which had, it is said, been inculcated in him by his parents and paternal grandmother. He read theology and studied the Bible constantly. He wrote on theology but apparently never published what he wrote. He was, during most of his life, a very devout Episcopalian. However, in 1839, after nine years of studiously reading theology, holding many serious conferences with theologians and studying the tenets of the Roman Catholic Church, he left the Episcopal Church and joined the Catholic Church. One of the reasons he gave for this was that in the cholera epidemic in 1832, the priests and sisters of charity of the Catholic Church attended the sick, while the other ministers fled in dismay from the dread pestilence. Since these members of the Catholic faith were willing to brave death in doing their duty, he felt that any religion which resulted in its members practicing what they preached must be the closest to the true Christian doctrine.

On October 26, 1820, Dr. Horner married Elizabeth Welsh, the daughter of John Welsh, a very prominent merchant of Philadelphia. They had ten children. He was a devoted husband and father and his family life was extremely happy.

Dr. Horner kept regular hours, arising at five A.M. He slept only six hours, and started each day with prayer and reading the bible. He counted each hour as lost which did not add something to his store of knowledge.

Dr. Horner apparently had an exterior life which appeared clear, bright, calm, and prosperous. But from his diary, which was conscientiously kept, it appears that his interior life was dark, despondent, and agitated with vague apprehensions, and that every mental effort was a conflict, a struggle and a victory.

His health was not good during most of his life. He writes in his diary of having a headache or a dull pain in his head for three fourths of his life; seldom acute but such as to make him uncomfortable and prefer solitude to company. In 1841 he first suffered with dyspnea and probably early cardiac failure, which was followed by swelling of the lower extremities.

Dr. Horner died on March 13, 1853. He had been seriously ill and extremely depressed for two months, but in spite of his weakened and precarious condition, two days before his death, he assisted in the examination of his students. The end came from a rupture of the intestines and peritonitis. And as was stated in the newspaper obituary, the City of Philadelphia suffered "a public calamity" and a great and good man had passed to his heavenly reward.

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President's Address

By RICHARD A. KERN

THIS meeting marks the close of the one hundred sixty-eighth year since the founding of this College. The constitution directs that "the President shall have general supervision of the affairs of the College, maintain order at the meetings, and deliver an Annual Address at the Stated Business Meeting in January." Custom has established that the Address shall take the form of a Report on the State of the College. Moreover, since my three-year term of office ends in this meeting, this Report is also an account of my stewardship, with some apologies for things unfinished and hopes deferred, and a few thoughts for the future.

FELLOWSHIP

The Fellowship has again shown an increase during the past year. In December, 1953, the total number of Fellows was 998. In December, 1954, there were 1047 Fellows, of whom 951 were Resident, 88 Non-Resident, 4 American Honorary and 2 Foreign Honorary Fellows.

DEATHS

Death has taken from us during the past year 15 Resident Fellows, 1 Non-Resident Fellow and 1 American Honorary Fellow. As I read their names, the Fellows will please to stand.

Resident Fellows

G. Mason Astley
Sidney G. Biddle
Ralph Butler
George H. Cross
John Eiman
Jaques P. Guequierre
Charles R. Heed
John E. Hume
Rutherford L. John
Balduin H. Lucké
Edward F. McLaughlin
Norman Rothschild
Hunter W. Scarlett
Francis W. Sinkler
George B. Wood

Non-Resident Fellow

John H. Jopson

Honorary Fellow

John Alexander

THE STAFF

I am pleased to report that there have been no deaths and few changes in our Staff. Dr. McDaniel, after a 4-months' leave of absence at his own request, has resumed his duties as Curator of the Library's Historical Collections. He has asked to be relieved of the editorship of the *Transactions*, a request that was granted by Council with regret because of the outstanding performance of that task by Dr. McDaniel during eighteen years. I take this opportunity to pay him my grateful tribute and a sailor's highest praise, "Well Done!" Mr. Morse has had a busy year as Librarian, as Secretary of the Hall Committee and in as-

sisting many of us with facts and statistics about the College for use in Fund raising. Mr. Beatty, who is in charge of the Reading Room, has just been appointed Editor of the *Transactions*, in which post he will have the advice and guidance of Dr. McDaniel. Mr. Allen, the Superintendent of the building, has continued his program of painting and repair in addition to routine care of our property. It is again my pleasure to note that under such devoted and efficient stewardship, the condition of our building and its contents is at its best in my experience.

At this point I wish to pay high tribute to our entire Staff, not only for their efficient performance of every routine duty or assigned task, but for their loyalty, devotion and dedication which they have so freely given to the College. Dr. McDaniel, Mr. Morse, Mr. Allen, Miss Lang, Mrs. Wade, Mr. Beatty, Miss Hodge, Miss Magasich, Miss Zeldis and every other member of our Staff (I wish there were time to mention every one by name) have each earned our deepest gratitude. I express my particular thanks to Miss Lang, whose help in and out of hours I have so frequently invoked, to whom I have assigned countless chores beyond her daily work, and who has done all these things well, cheerfully, and in spite of the handicap of a broken arm.

MEETINGS, SECTIONS AND COMMITTEES

In the number of the *Transactions* carrying this address will be published the List of the College Lectures presented at our Stated Meetings during the past year; also the Transactions of the several Sections, and the reports of a number of our Standing Committees. The programs of the Section Meetings maintain a high order of excellence. The Section on Medical History has again arranged for the first year students of the Philadelphia Medical Schools a series of six Lectures on the history of medicine by Professors Shryock and Temkin of Johns Hopkins University. I particularly recommend that you read the Reports of our Standing Committees: they will give you an insight into the manifold details of the operation of this College, and at the same time will prove to you how efficiently and well these committees have served you.

The College and the Philadelphia County Medical Society have continued to hold two joint meetings yearly, a commendable arrangement that has proved its merit to both groups. In addition, during 1954, the Philadelphia County Medical Society also held six of its Stated Meetings in this building, in order that its members might avail themselves of the better parking facilities. Such cooperative efforts between the College and the County Society should be fostered, and their extension deserves to be further explored.

PRE-MEETING SUBSCRIPTION DINNERS

An increasing number of Fellows are making use of the convenience of dining at the College before our evening meetings. As many as 78 have been so accommodated in the Hutchinson Room. During the past year this service has been extended by being made available to several societies which meet in the building: the Neurological Society, the Roentgen Ray Society, the Heart Association of South Eastern Pennsylvania, and to our own Section on Medical History. The Cadwalader Room has been used on one such occasion and can easily seat 125 diners. A suitable rental of such spaces provides additional income.

A NEW ENDOWED LECTURESHIP

Endowed Lectureships now provide a full quota of outstanding speakers for the Stated Meetings of the College. But the programs of our Sections could be strengthened if the Section officers had at their service a number of such lectureships. I am therefore pleased to announce that one of our Fellows, Dr. Kehar S. Chouké, on December 27, 1954, gave to the College the sum of $2000, to which he promised to add an equal amount in 1955, to endow a Lectureship in memory of his father, Hira S. Chouké.

ALVARENGA PRIZE

The Alvarenga Prize was awarded on July 14, 1954, the 71st Anniversary of the death of the

Testator, to Dr. DeWitt Stetten, Jr., Associate Director in Charge of Research, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md., for his outstanding contributions to our knowledge of metabolic diseases. At the October, 1954, Meeting of the College he presented the Alvarenga Prize Lecture, which will appear in the February, 1955, number of the *Transactions*.

MÜTTER MUSEUM

The Mütter Museum continues to attract a growing number of visitors, over 1800 last year, thanks to the excellent publicity which the Curator, Mrs. Ella N. Wade, has given our Collection in her articles appearing in *Philadelphia Medicine*. She has now written 67 such articles, 22 of which were published in 1954. Only last week I had occasion to leaf through the Register of Visitors, which showed more signatures of persons from near and far in the past year than ever in previous years, and they included groups of students from colleges, schools and hospitals.

PORTRAITS OF PAST PRESIDENTS

There are still six gaps in our collection of portraits of past presidents. Steps are now under way to fill at least one of these gaps during the current year.

PRESENTATION OF GAVEL

At the March meeting of the College, Dr. George E. Pfahler, our Fellow, presented to the College a beautiful gavel carved out of mastodon ivory recovered in Alaska; it is the one I am using this evening. The gavel is contained in a fine box with a silver plate on the lid carrying engraved the names of all the presidents of the College since its founding and with space on a similar plate on the inner surface for the names of future presidents for another couple of centuries.

THE LIBRARY

The Library continues to grow in size and usefulness, in spite of the crowded state of our stacks, and the limitations of our budget. Some 13,000 visitors consulted over 41,000 volumes from the stacks and an unknown number of books and journals on the shelves of the reading rooms. There were borrowed during 1954 over 10,200 volumes. The Library supplied 3714 photostats and loaned 3462 volumes to 126 libraries in 28 states, the District of Columbia and 4 provinces of Canada. Books accessioned during the year numbered over 2800, and there were received 1930 serially issued publications. In most of these services, especially those to other libraries and to borrowers in other cities, the figures show substantial increases over the previous year's figures. But please note: to find shelf room for the new material, older books had to be piled in passageways.

THE BUDGET

The Budget for the ensuing year, which you adopted this evening, again shows how closely we must guard our resources. Our anticipated expenditures total $102,618.48, our anticipated income from all sources is a very little more than that. In all our history our budget has always been in the black. But to keep it there, we have had to restrict purchases of desirable publications and to defer salary adjustments and necessary repairs.

THE FUTURE OF THE LIBRARY

Crowded stacks and an inadequate income raise the problems of a new stack building and additional endowment. Since its founding, the College has occupied three buildings. This one, our third, was erected in 1909, and since then has neither been enlarged nor submitted to any major repairs. In the 1920's, when money might have been raised, there was no urgent need for it. The depression and then the Second World War precluded action, even though the need was growing. Then, within a very few years these things happened: after the war there occurred a great increase in the output of all kinds of medical publications; as a result, our stacks were filled far sooner than had been anticipated; worst of all, the inflation

of our currency sharply reduced the purchasing power of our limited income.

In January, 1948, the President, Dr. J. Parsons Schaeffer, appointed a committee under the chairmanship of Dr. T. Grier Miller, to study the needs of the College and to collect funds to implement that study. Its result was a clear statement that the College, in order to continue to support a first class library, must increase its funds to purchase publications, increase the space to house them, and increase the endowment to maintain both. A program was outlined that included the erection of a new stack building that would double our storage space, a modernization of the present building and the collection of adequate endowment. Our sights were set high: $750,000 for building, and an equal amount for endowment. The collection of funds began actively in 1949, and has continued ever since. Progress was steady but slow. At the end of nearly 5 years, we had collected only $131,000. True, several foundations had expressed an interest in our problem and two had made tentative grants, but only on condition that we first raise well over a million dollars.

Then, in November, 1953, a prospective donor pointed out to us that our program needed to be speeded up lest further inflation do us yet more harm, and made the offer that if we would raise a total of $400,000 by December 31, 1954, we would receive $100,000, provided further that we begin work early in 1955. Here at last was a goal that seemed attainable. This was the challenge that I could announce to you just a year ago.

The year 1954 was the busiest one in regard to fund raising that the College has ever known. Not only the Fellows but the friends of the College have worked at an ever increasing tempo. A most significant fact that soon became clear was this: the more we ourselves gave, the better were we able to enlist the help and money of others. By the first of June we had nearly $176,000. But with the summer, all interest seemed to flag again, so that on the 20th of September the score stood at $195,000, or $205,000 short of the goal.

Then in close succession, three things happened.

On September 30th, the Donner Foundation of Philadelphia, whose interest in the College had first been enlisted by Dr. T. Grier Miller to the extent that 3 years ago they promised us $100,000 if we first raised $1,250,000, now lowered that provision to $400,000.

Then, on October 2nd, the Kresge Foundation of Detroit, which also had tentatively made a grant contingent on our raising well over a million dollars, advised Mr. Martin W. Clement, who had pleaded our cause with that group, that it too granted us $100,000, if we first raised $400,000, and on condition that our building be free of debt upon completion.

Finally, on October 5th, the anonymous donor, upon learning of these two grants, informed us that we could have the $100,000 forthwith, provided that we start work as originally stipulated, early in 1955. That meant that as of October 5th, we had to raise $105,000 by December 31st, in order to get the $200,000 from the Donner and Kresge Foundations.

This threw our machine into high gear and there it has been ever since.

Of particular help have been our Committee of Advisors: notably Mr. Clement and Mr. John Diemand with whom we have met repeatedly and who, in turn, ably assisted by the other members of that group: Messrs. Charles S. Cheston, J. Hamilton Cheston, Albert M. Greenfield, Edward Hopkinson, Jr., P. Blair Lee, Al Paul Lefton, Lawrence Saunders, Geoffrey S. Smith, Leon C. Sunstein and George E. Whitwell, invoked the help of many individuals and institutions of this area. On November 30th, when we still had $69,000 to go, these gentlemen arranged a dinner to which they invited over thirty guests of high financial rating to whom your officers were permitted to present the cause of the College.

During the waning weeks and days of the year, you were kept informed of the progress of events. You in turn buoyed up our hopes by your checks and your efforts with others. By December 13th, we still had over $50,000 to go. That is when the last frantic appeal to you

began, and you responded magnificently. I can't find words adequate to express my appreciation to you for all that you did. But even more do I value your letters and messages of hope and encouragement: I shall treasure them as long as I live.

It was almost a photo-finish. In a year-long race, we overtook our quota on the afternoon of December 29th. That same evening Dr. Jesse Nicholson brought to my home a letter from a friend of his, informing the College of a gift of stock worth $5000 that put us yet farther ahead. Indeed, thanks to an avalanche of checks from all of you, we finished on the 31st of December far out in front and going away, more than $12,000 in the lead.

Therefore on the 29th I could notify our anonymous benefactor that we had fulfilled our bargain, and on the 31st, anonymity was set aside and the Pew Memorial Foundation gave us its check for $100,000. This made it possible to contact the Donner and the Kresge Foundations, whose gifts should be in our hands within a few days. Counting these gifts as cash, the final score of our campaign as of this afternoon is as follows:

Cash raised:	$612,531.02
Pledges:	$28,193.33
Grand Total	$640,724.35

I wish to tell you some significant facts about our Campaign. During 1954, there were received gifts of $2,500 or more as follows: Mr. Charles H. Woodward, $2,500; Mr. George Woodward, $2,500; The Philadelphia Savings Fund Society, $3,500; The Indemnity Insurance Company of North America, $3,500; Mrs. Emory McMichael, $5,000; The Penn Mutual Life Insurance Company, $5,000; The Provident Mutual Life Insurance Company, $5,000; The Philadelphia Electric Company, $5,000; The Smith, Kline and French Foundation, $5,000; Mr. Clarence M. Brown, $5,025; A Friend of the College, $5,087; The Insurance Company of North America, $6,500; The Pew Memorial Foundation, $100,000: a total of $153,612, and *92 per cent of this was given in the last 5 weeks.*

These figures are imposing, but they were made possible only by the prior giving of our Fellows. Eighty-two per cent of you have now contributed, many of you several times. But you didn't get your steam up until the very last lap. Before October 5th, 1954, only 590 Fellows had made or obtained a gift. Since that date, 602 Fellows have participated: more in the last 3 months than in the 6 preceding years.

A fund-raising project requires the expenditure of two things: *money* to organize and publicize the project, and *effort* to collect the funds. Busy people are often inclined to shy at expending any effort, but instead prefer to pay professional fund raisers to do the work. They often overlook one important item: that the professional fund raisers have a way of skimming the cream off the top of the best prospects in the early days of the campaign and then leave the members of the organization holding the bag. I am sure all of us have learned this in our own experience and to our sorrow. Nevertheless, at the beginning of our program we consulted with our advisors as to the expediency of engaging a professional fund raiser, and they wisely pointed out that it would be difficult to make an emotional appeal to a wide public on behalf of a library: it is hard to dramatize a pile of books. And so, we decided to carry the ball ourselves.

Now the proposition, that it takes money and effort to raise funds, has this important corollary: the money expended and the effort employed stand in an inverse relationship to each other: the more effort, the less money it takes.

All this is by way of preface to this statement: in the 6 years of our campaign up to November 15th, we spent approximately $7500.00. During those years the funds which had been collected were invested in short-term low-interest securities that have yielded an income of $9700.00. That means that the $612,531 which we now have include every dollar that was collected, plus $2,200 of earned income. This sets something of a record in contemporary fund-raising.

Now to get back to the building program.

A stipulation set by the Pew Memorial Foundation is that we begin work promptly in 1955. Feeling confident that we would raise the money, and in anticipation of meeting that stipulation, the Council engaged an architect, Mr. Robert McGoodwin, to study our project and make a tentative estimate of its cost.

The project now consists of (a) a *new stack-building* at the back of our lot and continuous with the present stack-building, that will approximately double our stack space; and (b) a *rehabilitation of the present building.* The latter includes as its chief items: a new heating plant (which will occupy much less room than does the present one, and so make available some much needed space in the basement); new air-conditioning equipment, especially for the book-stacks; a passenger elevator between the first and second floors of this building; new wiring and lighting fixtures where needed. The estimated cost of this is between $565,000 and $575,000, well within the sum of money that we have raised. Accordingly, and as recommended by our Advisory Committee headed by Mr. Clement and Mr. Diemand, Council on December 3rd, 1954, authorized Mr. McGoodwin to proceed with final plans and their execution.

On authorization of the Council, and after conferring with the incoming president, Dr. Scheffey, I appointed a Building Committee, consisting of Dr. Jonathan E. Rhoads (the incoming Vice-President) as Chairman, Dr. T. Grier Miller (Past-President), Dr. Lewis C. Scheffey (incoming President) and myself as members. This committee has been meeting once a week with the architect and we can assure you that plans and specifications are rapidly taking form and that bids will be asked for and contracts considered next month.

INCREASED ENDOWMENT

The next major objective that we must achieve is *additional Endowment.* This should equal the cost of the *new* construction (not the rehabilitation of the present building), that is, about $300,000, plus a cushion for future needs of about $100,000, or a total of $400,000.

Let me point out that we already have a start in this direction. Of the $600,000 that have been raised for the building fund, it is hoped that at least $25,000 will be available for Endowment (indeed, the Donner Foundation specified that any unexpended balance of its $100,000 gift shall be applied to endowment).

In addition, we already have cash ($12,531.02) and pledges ($28,193.33) totalling $40,724.35, the amount by which we went over the top in the building fund drive.

Then there is the *James Harold Austin Memorial Fund*, begun in April, 1952, which now stands at $1,749.21.

Furthermore, the entrance fees of newly elected Fellows accrue to the Endowment Fund. In the 6 years that we have collected for the Building Fund, 365 new Fellows have thus added $18,250 to our Endowment.

These several items now add up to $85,753.56, or 21 per cent of our objective of $400,000.

The following steps are now being taken to secure additional endowment: Through the good offices of Mr. Malcolm Adam, President of the Penn Mutual Life Insurance Company, Dr. Alvin C. Eurich, head of the Ford Foundation, became interested in our problem and with Mr. Adam, Mr. Clement and Dr. Miller, visited the College last fall. On December 16th, he arranged a luncheon in New York City to which were invited representatives of the Rockefeller Foundation, the Carnegie Corporation, the Grant Foundation, the Commonwealth Fund, the John and Mary Markle Foundation and the James Foundation of New York. On that occasion Dr. Miller, Mr. Adam, Mr. Clement and I were given the opportunity to plead the cause of the College before them, and since that time each of these Foundations has been formally approached on behalf of the College.

Our Committee of Advisors, led by Mr. Clement and Mr. Diemand, having helped us over the top with the Building Fund, are now conducting an active and sustained campaign in business and financial circles in this city in the interest of the Endowment Fund.

Your officers will continue to make the

Endowment Fund their major interest in the months and years ahead. They deserve your fullest support.

In April, 1954, after the death of an old friend, it occurred to me that, in addition to my making a small contribution to the Building Fund in his memory, rather than sending flowers to his funeral, it might be possible to extend this custom and to make it more meaningful by having the memorial perpetuated by an entry in a suitable *Book of Remembrance*, and by an official letter from the College to the family of the deceased, advising them of the memorial gift and its donor. Council gave its approval and for eight months this plan has been in operation. In that time, 35 persons, including friends as well as Fellows of the College, have made contributions. The individual contributions have ranged in amount from $5 to $2,500. The total of such memorial gifts since last April is $9,816. Up to now, by decision of Council, all such memorial gifts have been added to the Building Fund. From now on, they should accrue to the Endowment Fund.

In recent months, as I sweated ink on behalf of the Building Fund, I used to think how much easier it would have been for us today, had there been a sustained program of soliciting gifts from Fellows over the years since 1909 when our last fund raising had ended. It follows logically that it would be a fine thing for future generations of Fellows if we started such a program now. Accordingly, Council approved the addition to the form, currently used for billing Fellows for their annual Contributions, of two additional lines: *Here is my voluntary contribution to the Endowment Fund*, and *Here is my voluntary contribution to the Building Fund*. This is a modest beginning of a sustained program (if an annual reminder deserves that name) to solicit yearly gifts for *future* needs. The term *Building Fund* as here used calls for definition: money so gathered should be invested and its income added to principal, the principal in turn to be used to pay for future new construction or for major repairs of such magnitude as to exceed, say, 25 per cent of the yearly budget. It is recommended to Council that it adopt some such provision.

Each year I have called to the attention of the Fellows the desirability of remembering the College in their wills. Legacies have been the chief source of our endowment, now valued at over $1,000,000. Yet another year has passed, in which 17 Fellows have died, and none saw fit so to remember the College. Indeed, no legacy has been received by the College in the 6 years during which I have been an officer. Surely, most of us could make provision for some such bequest without detriment to our families. Moreover, it would be a better thing for the College to receive ten small bequests rather than a single large one.

One final thought: I have been impressed that with the growing numbers of our Fellowship the College has become so large that the officers lose the personal touch with the majority of the members. In trying to offset this in a measure, I resorted to sending out some mimeographed messages about our Fund Drive several times during the year. It would seem that in this simple and inexpensive way, not only the president but other officers and Councillors could bring much information about the College to our Fellowship, and so kindle a greater interest and participation in the affairs of this great institution.

Now let me express my sincere thanks to the Fellows of the College for the great honor of its presidency during the past three years. It has been a challenging and stimulating experience that I shall remember very pleasantly. Above all, it has been a rich and rewarding experience in the friendships made and fruitful service shared with all of you: officers, members, and staff, with whom it was my privilege to work.

And now to you, Dr. Scheffey, and you, Dr. Rhoads, my congratulations upon the opportunities that lie before you, and my best wishes for as interesting and happy a tour of office as it was mine to enjoy; nay, an even happier one, for you will see as accomplished facts things that today are still in the realm of dreams.

REPORT OF THE TREASURER FOR THE YEAR ENDED NOVEMBER 10, 1954

Assets

Cash in banks and on hand				
General fund			$6,236.15	
Trust fund balances of income (restricted)			19,962.86	$26,199.01
Assets held in trust funds and mortgage secured by North East Corner 13th and Locust Streets property				
Mortgages			57,020.38	
Bonds			265,462.37	
Preferred stocks			297,648.31	
Common stocks			384,875.89	
Principal cash for investment			83,545.21	1,088,552.16
Property				
Land—15–25 South Twenty-second Street			95,000.00	
Building			782,500.00	
Furniture and fixtures			1.00	877,501.28
Deposits on perpetual fire insurance policies				9,521.28
Total				$2,001,773.45

Liabilities

Unexpended income				
General funds				
Library general account			$922.02	
Life membership account—uninvested portion			391.64	
Reserve for contingencies—uninvested portion			290.02	
Operating fund balances				
Current operating account		$3,558.99		
President's room		525.00		
Publication committee		316.78		
Friends of library		20.00		
Pension reserve		276.96		
Entertainment committee		161.59		
Rare books account		152.96		
Less: Overexpended balances		5,012.28		
Harvey's "De Motu Cordis" Facsimile 1628 edition	$202.18			
Books	29.53			
Campaign expense account	112.10			
Portrait account	36.00	379.81	4,632.47	$6,236.15
Trust funds—income				
Discretionary common trust fund			17,054.68	
Legal common trust fund			663.78	
Trust funds not pooled			2,244.40	19,962.86
Special account re: purchase money mortgage secured by Northeast Corner 13th and Locust Streets property			54,000.00	
Trust funds—principal (book values)				
Discretionary common trust fund			767,290.08	
Legal common trust fund			23,500.88	
Trust funds not pooled			17,873.09	
Maintenance and reserve fund			17,626.05	
Fellows' building fund			103,247.16	
General contributors' development fund			103,498.69	
J. Harold Austin memorial fund			1,516.21	1,088,552.16
Plant fund				887,022.28
Total				$2,001,773.45

Statement of Income and Expenses

Income		
On investments net of agent's fees		
Trust funds	$43,743.64	
Income funds, principal of which is not administered by the College of Physicians of Philadelphia	600.20	
Mortgage	2,496.28	$46,840.12
Contributions		
Fellows' dues	44,365.00	
Life membership	879.00	
Entrance contributions	3,150.00	
Use of halls and projector	2,923.00	
Miscellaneous contributions	1,401.86	52,718.86
Library		7,847.44
Miscellaneous		1,346.88
Total income		108,753.30
Expenses		
Operating expenses		
Hall Committee	20,261.04	
Office of the Secretary	5,311.88	
Office of the Treasurer	5,167.05	
Pensions	4,225.68	
Campaign expense	1,200.44	
Publication Committee	3,173.34	
College Collections Committee	2,898.42	
Books	1,840.01	
Entertainment	925.22	45,003.08
Library		
Salaries and payroll taxes	36,538.24	
Books, journals, supplies, etc.	18,114.18	54,652.42
Restricted trust funds		
Discretionary common trust fund	7,252.92	
Legal common trust fund	1,055.09	
Trust funds not pooled	380.55	8,688.56
Total expenses		108,344.06
Income in excess of expenses		$409.24

Notes: Receipts of special purpose funds from contributions and security investments not included in the foregoing schedule were as follows during the fiscal year ended November 10, 1954:

Fund	Amount
Maintenance and reserve fund (Income)	$220.00
Fellows' building fund (Contributions)	30,740.34
General contributors' development fund (Contributions)	58,900.11
J. Harold Austin memorial fund (Contributions)	115.00

Francis C. Grant
Treasurer

Annual Report on the Library*

ADMINISTRATIVE

The Book-Selection Policy

Last year's annual report considered the policies governing the choice of the journals regularly received by the College of Physicians Library. This year's report directs itself to the process of book-selection. The position of the book in medical literature will be considered. The general factors common to book-selection in all libraries will be related to the College library. Some of the available guides to medical book-selection will be discussed. Specific criteria for judging individual titles will be presented in the light of the College's acquisition program.

Objectives of this Report

This report proposes to describe the present book-selection policy and the factors which have determined it. It is expected that the Fellows of the College and other readers of this report will be better able to judge what types of material should be found in the library. The library administration hopes to have clarified its own thinking by formulating this statement. Finally it will provide a basis for study if a reevaluation of the policy appears to be needed.

The Medical Book

Because this report deals with the selection of medical books, it is fitting that it begin with a brief analysis of the position of the book in modern medical literature. This seems especially appropriate because the book is so often compared unfavorably with the journal as a means of presenting scientific information.

The basic literature of any science is to be found in its textbooks and monographs. Without summaries, histories, and reviews, there would be no control or perspective of the literature. The process of learning all that is known about even the smallest area of investigation would become laborious and inefficient. The day of the definitive treatise on a particular part of the body, disease, or method of treatment, is not over. Such volumes serve as landmarks or jetties between which the sands of research settle comfortably into place.

The most obvious advantage offered by the book is the space which it offers to the investigator with a significant amount of original clinical or research material. A complete presentation of his case records, statistics, or other data, his research methods, and his conclusions are necessary for other investigators of the same or allied problems who wish to make comparisons with their own findings and to make critical evaluations of the conclusions. Such basic accumulations of information are commonplace in this era of subsidized research.

Fortunately for librarians, a large degree of selection has already been made by the book publishers. Mr. Walter Kahoe, Director of the Medical Department of the J. B. Lippincott Company, estimates that 20 manuscripts are rejected for every one published. He believes that the books which are actually published have been so carefully screened that no librarian can afford not to consider every medical book issued by a major publisher.[1]

The journal may well be the life blood of medical literature, but without the skeleton provided by the book, this literature would be an amorphous mass.

Quantity of the medical book literature. It is the sheer mass of today's medical book production which makes selection a practical problem. To the best of our knowledge, the Armed Forces Medical Library is the only library which attempts to acquire all of the medical literature published. This policy has been declared as follows, "to gather the whole of medical literature, wherever and whenever

* 1 November 1953–31 October 1954.

[1] Unpublished paper presented at the meeting of the Philadelphia Regional Group of the Medical Library Association, January 20, 1955.

published, without regard to language, authorship, quality, or any other of the factors of selection which condition most library collecting."[2] All of the other libraries are faced with the very real problem of deciding which books to acquire and which books to reject.

Recent studies have drawn attention to the terrifying quantity of journal literature being produced in the medical sciences but less attention has been given to the actual number of books published. In the journal field it is known that there are 3,908 titles listed in World Medical Periodicals (Paris, WHO and UNESCO, 1953), and 12,624 titles listed in Periodica Medica (4th ed., Stuttgart, Thieme, 1952), and that there are 6,776 titles in the List of abbreviations for serial publications used in the Fourth Series of the Index Catalogue (Ser. 4, vol. 10: pp. 1–138, 1948).

For the purposes of this report, an attempt has been made to suggest the magnitude of the medical book production in the English language in English speaking countries during 1953. The book has been considered to be the non-journal part of the literature including pamphlets, monographs in series, and annuals. A fairly broad concept of what constitutes "medical" has been adopted because of the variety of subject matter reviewed or listed in the *Journal of the American Medical Association* which was one of the sources of titles. However, material added from other sources does not include such borderline subjects as: anthropology, botany, inorganic chemistry, medical fiction, physical chemistry, physical education, psychology, sociology, and zoology, unless the title indicates a major interest in medicine.

In a summary of book production for 1953, *Publishers' Weekly* reported having listed 485 new books and new editions in the field of medicine and hygiene.[3] An actual count, which included pamphlets as well as books, of the medical items which appeared in the "Weekly Record" section of *Publishers' Weekly*, produced a total of 777 volumes. The total cost of these volumes was $4,837.60[4].

When this report was written, 1,605 1953 English language medical books had come to the attention of the library. It is not to be assumed that this is the production for the year. The College library has acquired 699 volumes and has rejected 790 volumes. The remainder are on order or the decision has been deferred pending the receipt of further information.

General Selection Factors

The solution of the book-selection problem for a particular library is largely determined by four general factors. These factors are: the nature and purpose of the library, the limitations imposed by the budget, the staff time available for the processing of the material acquired, and the amount of space available in the library.

Nature and purpose of the College library. A descriptive leaflet issued by the library in 1951 said, "The functional development of the library is that of progression from a small collection for local, private use to a major research library giving local, national and international service to a wide public." Last year's report described the influence, on this library, of the highly developed spirit of regional cooperation in the Philadelphia area. A concentration on the central core of medical literature has been made possible by the existence of outstanding libraries in the metropolitan area in the related fields of the natural sciences, physical sciences, chemistry, dentistry, veterinary medicine, and pharmacy.

In the book field, the College library looks to the five Philadelphia medical schools for intensive coverage of medical education, textbooks, and other curriculum material. Medical schools affiliated with major hospitals are expected to cover the fields of hospital adminis-

[2] Grosbeck, Joseph. Some problems of scope and coverage. *Bulletin of the Medical Library Association*, **39:** 97 (April 1951).

[3] American book publication—1953. *Publishers' Weekly*, **165:** 275 (Jan. 23, 1954).

[4] 654 titles were found in 1953 issues of *Publishers' Weekly*. Additional 1953 imprints were listed in January-June 1954 issues.

tration and nursing more exhaustively than is necessary at the College. As a research library, complementing the other medical libraries in the area, it is assumed that the College library can contribute most effectively to the total amount of medical literature in the city by concentrating on research materials.

The College library's collecting program has also been influenced by the existence of the Free Library of Philadelphia and the Library of the Philadelphia County Medical Society. The field of popular medicine and medical fiction has been left to the Free Library. Books written exclusively for the general practitioner have been assumed to be available at the Philadelphia County Medical Society library.

Almost no book material has been acquired in those languages which do not use the Roman alphabet. This has been justified by the very small demand for this material and the proximity of the Armed Forces Medical Library, from which such material can readily be borrowed.

Financial limitations. In recent years the College library has been spending between $3,500 and $5,000 per year for the purchase of books. This has been considered to be an equitable share of the total library budget. Between 725 and 1,000 volumes have been purchased annually during the past five years.

By way of comparison, the following numbers of current books were purchased by the Armed Forces Medical Library; 1951 (9,387); 1950 (6,894); and 1949 (4,335). The expenditures for current medical books were: 1953 ($22,848.41); 1952 ($33,199.47); 1951 ($37,664.82); 1950 ($31,014.83); and 1949 ($19,222.17). The degree of selectivity required for the College library becomes apparent.

Staff limitations. To be effective, a library's books must be cataloged. The mere hoarding of books, whose presence in the library can be known only to a few persons, is pointless. At the present time there are three persons primarily engaged in the acquisition and processing of books acquired by the library. The professionally trained cataloger classifies the books and assigns the subject headings. She has the assistance of one person who types the catalog cards and processes new editions of older titles. This assistant is also expected to bind pamphlets and journals which are not considered worth commercial binding. The third person does the descriptive cataloging and accessions the books. In addition, this person is called upon for secretarial services to the Librarian and to the Curator, and sends out the book orders. All three of these persons carry a regular desk relief schedule which reduces the amount of time spent on their own jobs by about one quarter.

By way of comparison, the 1953 report of the Armed Forces Medical Library shows 29 persons employed in the Acquisition Division and 48 in the Catalog Division. During the year, 14,044 new titles were completely cataloged at the Armed Forces Medical Library. Such are the problems and dimensions of attempting an exhaustive coverage of the literature.

Certainly no expansion of the College's acquisition program is possible without an expansion of the present staff. In fact, it is extremely doubtful whether the present staff could be considered adequate quantitatively by any standards.

Space limitations. In December 1954, it became apparent that the College library would acquire space within the coming year for an estimated 170,000 additional volumes. However, the ten or fifteen years immediately preceding this happy event have witnessed overcrowded stacks that did not encourage an aggressive acquisition program. Even now, estimates of the period of growth provided by this addition are predicated upon the addition of not more than the equivalent of 5,000 volumes per year, including journals. With the space restrictions of a city lot all too apparent, this consideration will continue to be a limiting factor.

Book-Selection Guides

Mystic intuition and subconscious criteria which begrudge description undoubtedly play

a role in book-selection, but there is no want of printed aids for the inquisitive librarian. A more complete treatment of this aspect will be found in "A Handbook of Medical Library Practice" (Chicago, A. L. A., 1943).

Book reviews. The principal source of critical evaluations of new books is the book review. Journals which cover the entire field of medicine, whose reviews are widely read and heeded, are the *Journal of the American Medical Association*, *Lancet*, *British Medical Journal*, and the *New England Journal of Medicine.* Almost all of the leading specialty journals carry reviews of books in their own field. In other countries, national journals review their book production.

The reviewers in these journals are recognized authorities whose opinions are respected. Nevertheless, there is often a variety of opinion on certain titles which encourages further investigation on the part of the prospective purchaser. The major drawback to any considerable reliance upon the book review is the inevitable delay in its appearance. Libraries occasionally receive requests for books before they are published and often before authoritative reviews have appeared. In fact, the period of greatest demand may well be within the first year after publication.

Book lists. Book lists are a regular feature of most of the journals which carry book reviews. Such lists are generally more extensive than the number of books which can be reviewed and they enjoy the advantage of less time lag. Lists of books received are also issued by libraries; however, they cannot be construed as recommendations. Bookstores, agents, and publishers also issue helpful lists.

Committee advice. One of the traditional book-selection methods, which has not been fully exploited by the College library, is the advisory board technique. The atomization of knowledge in recent years has made it increasingly difficult to gather enough experts to judge the great variety of publications. Seeking library committee approval of every purchase would delay acquisition considerably and would be a tedious procedure for the committee. Members of the library committee are usually hesitant to pass judgement on a book unless it is in their own special subject field. The technique of a larger advisory board, representative of more subject fields, has been used by some libraries. Members of this board may be asked to pass on all books or may only be consulted in doubtful cases or for particularly expensive volumes. There is an understandable tendency, however, for the expert to want all of the material in his field. It is also difficult for the subject expert to gain a feeling for the entire collection and to judge the relative importance of his field to the subject balance of the entire collection. For these reasons the main burden of book selection for the College library, through the years, has fallen upon the Librarian.

Approval arrangements. Local bookstores are often willing to send books to the library for examination with the option of returning them. This device has not proven to be too helpful because of the delays in securing specialized advice and because of the small percentage of approval material which is retained. Transportation costs and bookkeeping complications offset the advantages of this method both for the library and for the bookstore.

Specific Book-Selection Criteria

Relation to the collection. Every book under consideration should be weighed in its relation to the existing collection. Is the book in a field which the library covers comprehensively? Ownership of a particularly strong subject collection carries with it the obligation to maintain its strength. In many instances such collections result from special endowments. Areas of subject strength in the College library are: dermatology, ophthalmology, radiology, obstetrics and gynecology, pediatrics, surgery, and medical history. In less intensively covered fields, a book may be rejected because it does not contain information not already in the library. In many cases, the recent purchase of a recognized text in a particular field will weigh against the addition of an equally distinguished text which appears shortly afterwards on the

same subject. A book which is the first to be published in a field is acquired even though the interest in that subject is limited. Purchasing in borderline fields is limited to outstanding books.

Demand. Book-selection cannot be performed exclusively in the Librarian's office. The members of the staff who have the most immediate contact with the library's users are in the best position to know what material is being requested and to acquire a good sense of the areas in which the collection is weak.

The notice, "Recommendations as to acquisitions are cordially welcomed by the library", has appeared regularly on the library's book list and on the monthly meeting notices distributed by the College. In order particularly to encourage Fellows of the College to make recommendations, it is the policy of the library to buy any volume suggested by a Fellow. It is true that a particularly active group in one field could distort the library's subject balance, but the advantage of having its informed judgement outweighs this risk.

In certain areas, the College library acquires material in spite of the absence of an immediate demand. This is especially true of foreign language books. Purchases are made out of proportion to demand because no other medical library in the region acquires any significant number. These libraries acknowledge their dependence upon the College library in this respect.

Clinical and research material. Volumes containing clinical or research material not previously reported are of special interest to a research library. The intensive investigation of a relatively small subject usually produces unique information in the form of case records, laboratory findings, or statistical analyses.

Authority. The deciding factor in the selection of a book is often the reputation of the author. The acquisition of every book written by men of international reputation is almost inevitable. The library also places great confidence in the prestige of the publisher. The standing of the institution with which the author is affiliated carries weight. All of the publications of the leading research institutions are sought.

Format. If the book under consideration is actually on hand, or if it can be obtained on approval, there are certain physical indications of its value. Bibliographies and indexes are clues to the care with which a book was published. The quality of illustrations, paper, and typography is seldom neglected in a good book.

Reference value. The College library has built a strong collection of medical dictionaries. Single language, bi-lingual, and polyglot medical dictionaries are ordered whenever noted. National directories and medical directories of the metropolitan area and the state are always acquired. Other reference tools such as bibliographies, indexes, and reviews are eagerly sought to facilitate answering the many reference questions which are directed to the library.

Specialized information. The proceedings of national and international congresses are systematically added. Many medical theses are received through exchange agreements and by the courtesy of neighboring institutions which do not collect dissertations. Reports of leading hospitals and national societies are received. A special effort is made to receive reports of all local institutions engaged in medical service and research. The needs of the historians of the future are constantly kept in mind.

The factors which enter into the library's selection of rare books are considered by the Curator of the Library's Historical Collections in the historical section of this report.

Conclusion

The book-selection policy described in this report has evolved over a long period of years. It has been determined by the position of the College of Physicians in medical research. It has been limited by the amount of space, money, and staff time available for the library.

This statement of policy should assist those persons who use the library extensively. It could form a basis for discussion with other Philadelphia institutions collecting books in the fields of the biological sciences. Finally, any long range planning for the future of the

College should evaluate the adequacy of the present acquisition program.

The College Library in 1953–1954

Building

The end of the library's report year came in the same exciting closing weeks of the College's campaign for funds for a library stack addition and for remodelling the building. This drive has now been successfully accomplished. The library administration and staff are thanking the library gods for providing such eloquent spokesmen, diligent workers, and thorough planners as Dr. T. Grier Miller, Dr. Richard A. Kern, and the late Dr. J. Harold Austin. The library joins the President of the College in his gratitude to the Advisory Board, the Fellows of the College, and the others who have given the library this new lease on the future.

Personnel

In order to spread administrative responsibility more widely, the library committee approved the appointment of two assistant librarians effective January 1, 1954. Miss Muriel Hodge, former Cataloger, was appointed Assistant Librarian in charge of the Preparation Division. Mr. William K. Beatty, former Reading Room Assistant, was appointed Assistant Librarian in charge of the Readers' Service Division. This broader sharing of the library's administrative responsibility has not resulted in any considerable revision of the library's routines. In fact, the continuing pressure of the many duties of the assistant librarians has prevented the fullest exploitation of the advantages which this development guarantees. It is hoped that time will be found during the coming year for a reevaluation of the library's facilities by this administrative group.

The primary responsibility for the administration of the Medical Literature Service, the Rare Book and Medical History Department, and the Serials Division, remains with the heads of these departments.

In conjunction with these changes there has been an expansion in the duties and responsibilities of the section of the library which services the current journal literature. Accordingly the title of the head of this department has been changed from Periodicals Room Assistant to Serials Librarian.

In further recognition of the added responsibilities of this department, the employment of an additional library assistant was authorized, effective April 1, 1954. In addition to strengthening the Serials Department, this appointment has the effect of somewhat lessening the amount of desk relief work required of the Preparation Division personnel. This assistant is also relieving at the Circulation Desk two mornings a week to give the Assistant Librarian an opportunity to perform tasks not otherwise permitted by the pressure of desk service.

One of the most exciting chapters in the library's history has been presaged by the appointment of Mr. W. B. McDaniel 2d as Curator of the Library's Historical Collections. Some of the problems relating to the development of a Rare Book and Medical History Department were given in last year's annual report. As a logical prelude to the initiation of this arduous task, the Curator was granted a four months sabbatical leave during the latter part of the year just closed. The appropriateness of this recognition after 21 years of unstinted service to the College is self evident.

Mrs. Elizabeth F. Bready, the Serials Librarian, resigned in August after nine years of devoted service to the library during which time she took a most active part in the work of the Medical Library Association, serving as Chairman of the Committee on Periodicals and Serial Publications, and editing the association's publication, *Vital Notes on Medical Periodicals*.

Miss Muriel Zeldis, formerly Assistant Librarian of the Hospital of the University of Pennsylvania was appointed to the Serials Librarianship. Her previous medical library experience and broad educational background have prepared her well for this responsibility.

Miss Margaret Greene has been promoted

from the position of Senior Page and Photostat Operator to the position of Serials Assistant. The library administration is pleased to have been able to recognize the excellence of her work during the four years of her employment in the library.

Serials

The library committee joined the library administration in two studies of the library's journal list during the year.

The list of journals regularly received was checked against the list of journals indexed in the January–June 1952 volume of the *Quarterly Cumulative Index Medicus* and the January–June 1953 volume of the *Current List of Medical Literature*. The library committee was supplied with a list of the 38 titles which were indexed in both guides but were not being regularly received by the College library. The committee was also told where these journals are abstracted and how many requests there had been for each title which the library had been unable to fill.

Two of these journals were considered to be out of the scope of the library. Ten of the journals which were published by societies were requested on exchange and the remaining titles were ordered from subscription agencies.

The second study was based on the subscription renewal order of the agent who handles most of the library's American and Latin American journal subscriptions. A list of the 29 subscriptions which were not indexed in either *Current List of Medical Literature* or *Quarterly Cumulative Index Medicus* was supplied to the committee along with an indication of the number of times each of the journals had circulated in a tabulation which had been made of 16,029 journal circulations. As a result of this study, the committee recommended the cancellation of six of the titles.

Serial records formerly maintained by the Preparation Division, have been transferred to the Serials Department. In this way all standing orders for periodicals, annuals, and monographic series will be centralized in one department.

The association file maintained by the Serials Department has been expanded to show whether or not the proceedings of the society appear in its journal.

The responsibility for recording information about the proceedings of congresses has been transferred from the Catalog Department to the Serials Department.

Announcements of congresses have been noted and, when considered important, letters have been written to the congress requesting announcements, programs, and proceedings.

Telephone Service

A tabulation was made of the number of incoming telephone calls during a three week period. This study showed an increase of 44 per cent over the number of calls received during a similar period in 1951.

Osler Library representation

The Chairman of the library committee, who is ex officio one of the Curators of the Osler Library at McGill University, represented the College library at the annual meeting of the Curators.

Professional staff activity

Miss Muriel Hodge is the chairman of the Program Committee of the Philadelphia Regional Group of the Medical Library Association. She is chairman of the Philadelphia Regional Group of the Division of Cataloging and Classification of the American Library Association. She also serves on the Program Committee of the local chapter of the Special Libraries Association.

Mr. William K. Beatty is chairman of the Employment Committee of the Special Libraries Council of Philadelphia. He is a member of the Medical Library Association's Committee on Periodicals and Serial Publications. He is also serving the local chapter of the Medical Library Association as a member of its Executive Board and of its Nominating Committee.

Mrs. Virginia Beatty is chairman of the Hospitality Committee of the Special Libraries

Council of Philadelphia. She is a member of the Medical Library Association's Committee on Periodicals and Serial Publications. She is also a member of the Membership-Hospitality Committee of the regional group of the Medical Library Association. Mrs. Beatty presented a report on the Medical Literature Service to the regional Medical Library Association group and to a conference of the Legal Medicine Institute of Philadelphia.

Mr. W. B. McDaniel's professional activities and writings will be noted in the historical portion of this report.

Mr. Elliott H. Morse is managing editor of the *Bulletin of the Special Libraries Council of Philadelphia*. He also served on the Program Committee of the Medical Library Association. Mr. Morse wrote an article on the College for the *News of the Graduate School of Medicine* and an article on modern Italian libraries for the *Encyclopedia Americana*.

Five members of the library staff attended sessions of the Medical Library Association which was held in Washington.

Benefactors

A list of the donors of books and other library materials appears in the statistical section of this report.

The library is pleased to be able to report the following institutional subscriptions to the support of the library made under the terms of the Contribution Plan:

Sharp & Dohme
Smith, Kline & French
National Drug Company
Wyeth Laboratories
McNeil Laboratories, Inc.
Air-Shields Inc.
Barnes, Dechert, Price, Myers & Rhoads
Chew, Harvey, & Thomas
E. I. du Pont de Nemours Experimental Station
E. I. du Pont de Nemours Haskell Laboratory
Freedman, Landy, & Lorry
Gray & Rogers
Hercules Powder Company
La Wall & Harrisson
MacAndrews & Forbes Company
Norwich Pharmacal Co.
Quaker Chemical Products Corp.
Richter, Lord & Farage
Riker Laboratories
Rittenhouse Book Store
Rohm & Haas Company
Samson Laboratories
Squibb Institute for Medical Research
Henry K. Wampole & Company, Inc.

Medical Literature Service

The Medical Literature Service, started just over a year ago, has become such an important part of the library's services that its director has been asked to write the following section of this report.

E. H. M.

MEDICAL LITERATURE SERVICE

The Medical Literature Service came into being on the first day of October, 1953. Its aims were to provide extended reference service for the users of the Library and to present a complete bibliographic service to the medical and allied professions in the area.

Mr. Allen, the Superintendent, was responsible for the repainting of the Packard Room and the refinishing of a handsome desk and chair which made possible the operation of the Service from centrally located quarters.

On February 1, 1954 the staff was doubled by the addition of Miss Jean Carr as a full-time assistant. The acquisition of Miss Carr has done more than any thing else to establish the Service. In addition the Service currently employs, on a part time basis, several translators and abstractors as well as a typist.

The facilities of the Service may be shown by a description of its work. Literature searches are conducted on both a current and an historical basis (18 current searches and 82 historical searches during 1953–1954). Bibliographies are compiled or checked, and annotations and abstracts are provided. Translations form an important part of the Service's work and 93 of them were done both into and out of some 16 languages during the past year. All medical translations are done by M.D.'s. The service examines every journal that comes into the library (some 1,700 in all) and sends out periodic reports on the current literature to seven subscribers on 18 subjects.

The Service is equipped to take care of the different requirements of the medical writer. In the past year the references to 17 papers were checked prior to publication.

During the past year the Service has done work for individuals from the undergraduate to the research level and for organizations such as pharmaceutical houses, clinics, hospitals, and educational institutions. Geographically, the area covered included the whole United States and several foreign countries.

The rapid growth of the Service seems to imply that it is filling a definite need.

V. L. B.

HISTORICAL

Selection of Materials

Following the Librarian's lead, and suggestion, there will be, first, an attempt on the part of the historical department to set forth briefly certain factors, including articles of faith, that at present largely govern the selection of materials to be added to our historical collections.[1] In the main, there are no significant differences of material factors or of targets operative in the selection of materials for the general collections and for the historical collections. Both areas bend the knee to a limited budget (which argues a limited personnel); to limited space; and to a crustaceous concept of the obligations of a research library in a community of research libraries.

Mammon. The historical department receives annually no more than approximately $38 in income from funds endowed in its favor. As was mentioned in last year's report, the library budget puts $1,000 annually at the disposal of the department for the purchase of primary historical material. Moreover, secondary texts are regarded, quite naturally, as coming within the range of normal demands on the general library budget. We have, too, fortunately, a loyal corps of individual and corporate friends to which we can turn when a pearl of great price would be lost to us without our resorting to open solicitation. Nevertheless, it will be clear to those conversant with current prices for primary historical material that purchased additions to the historical collections must be weighed only when the body heat is somewhere below room temperature, and preferably in accordance with a strategic plan—the dogma obtaining.

Dogma. If the library were unique in its field nationally, as it is in its immediate area, there would be reason indeed to propose an exhaustive study of its historical collections, area by area, for the purpose of making a concerted effort to build towards that chimera called 'completeness'. As things are, though unique locally, the library exists, as the Librarian has pointed out, in a complex of research libraries, several in contiguous fields, whose holdings and responsibilities we can no more conscientiously disregard in the historical area than in the general area. In the national context, the library breathes more or less in common with a handful of other medical research libraries whose holdings, insofar as there is public record of them, can also not be entirely unrelated to our ambitions, if these are to make economic and philosophic sense. If there is any truth in this for our general library, its application to the historical collections can still less be questioned. Affected by Mammon and dogma, though in varying ways or degree, are both our purchases and the gifts generously offered to us.

Purchases. The library has a fine collection of incunabula, which it properly values. There are finer collections of these 15th century publications in the country, however; and it is questionable whether, from a medico-historical research point of view, the collection of these expensive texts, unless thoughtfully controlled, serves a valid purpose today. We do not now purchase an incunable merely to add to the incunabula count. The text must first of all have a clearer specific relationship to medicine

[1] For comparative data, see the illuminating paper, "Recent Trends in Medical Historical Libraries of the United States", by Gertrude L. Annan, Assistant Librarian, New York Academy of Medicine, recently published in the *Proceedings of the First International Congress on Medical Librarianship.*

pur than many of our incunabula can boast, acquired as they were when the incunabula fever raged widely over the country, with some consequent relaxation of scholarly purpose. We look with the warmest stirrings of desire on a medical, or heavily medicated, text or edition that appears not to be represented in any other collection in the country, even though a facsimile reprint may be available in the library. If there are four or five 15th century editions of a genuinely medical text, if no collection in the country has a complete set of them, we welcome an opportunity to provide a complete set in our collection. The same holds in respect of the 15th century printings of the writings of a given medical author. There are, of course, other, less obvious, relationships that would lead us to purchase an incunable; but those just suggested may serve to illustrate what would once, certainly, have been regarded as a program of Catonian austerity.

In the field of manuscripts, ancient, medieval, renaissance, and later, our thoughts have not taken quite such specific form. In general, as one may suppose, the indicated material factors and high moral climate tend to make us think here also in terms of potential usefulness rather than of ornament. Our ability to abide more or less faithfully by these criteria stems, of course, from the existence of published lists of American holdings of incunabula and medieval and renaissance manuscripts.

The somewhat artificially rarified atmosphere of the incunabula and manuscripts being thus perhaps too summarily disposed of, what of the vastly larger area of medical publication that confronts us beginning with the year 1501? Here, again, we are faced with some very respectable and valued sacred cows, to which we have also, except in the last instance, bibliographical guides: for instance, 1) Garrison and Morton's "Medical Bibliography: a Check-list of Texts Illustrating the History of the Medical Sciences"; 2) Pollard and Redgrave's "Short-title Catalogue of Books Printed in England, Scotland, and Ireland, and of English Books Printed Abroad, 1475–1640", with Bishop's "Checklist of American Copies of 'Short-title Catalogue' Books", and Wing's "Short-title Catalogue of Books Printed in England . . . , 1641–1700"; and 3) the uncodified category known as Americana Medica.

The researcher often starts from such a bibliography as that of Garrison and Morton. The words "Garrison-Morton Classic" in a dealer's catalogue turn our steps automatically toward our own catalogue—though we know that we are likely to find the work listed therein. Pollard and Redgrave, and Wing, are comprehensive general catalogues with non-comprehensive and sometimes insecure coverage of holdings; Bishop, while extremely helpful in respect of American holdings, suffers to some extent from inexpert American checkers' handling of the *S. T. C.* entries. References, in the dealers' catalogues, to *S. T. C.*, *Bishop*, and *Wing* have, therefore, no clearly compelling value to us. The work offered must pass further examinations for graduation.

As for the Americana Medica, our thought is first, naturally, to lead in material applicable to the medical history of our own area; then to increase as intensively as possible our resources for studies of American medicine as a whole or in other geographical areas. If a cache of manuscript letters written by American physicians of the early 19th century is offered to us for sale (or even as a gift), the letters having specific application to New York and Philadelphia medicine in a ratio of 5 to 1, the Philadelphia letter is promptly acquired (if possible), the New York letters being regarded as not acceptable unless they have been rejected by the appropriate institutions in that city or state. Common practice, this, among many contemporary historical custodians, but not always as well known to their constituents and to dealers as it might profitably be.

In areas not governed in some degree by authoritative guides, the purchasing situation inevitably becomes even more subjective. Except for the Armed Forces Medical Library, we have too little information on the historical holdings of the other great medical libraries. The Philadelphia Union Library Catalogue

serves excellently to prevent unnecessary duplication on the local scene, and, drawing on the National Union Library Catalogue, could doubtless serve us to some extent on a wider scale. But when we do not know the relative strengths of our sister institutions in this historical division and that, purchases of rare material must often be made on a more speculative basis than is economically desirable. In our general library, the great majority of book and journal purchases would have to be made regardless of the existence of local and distant duplication. But time is usually less urgent in the historical field. With microfilm, the photostat—and, to a less degree than in the general field, the inter-library loan—available, geographically ill-placed duplication of expensive material appeals to the scholar as a worthy take-home problem for us curators of historical materials. Our purchases, here, in the nationally uncharted areas, are concentrated quite naturally on strengthening the cell known to be strong and the neglected cell with current and future promises of usefulness; and on avoiding duplication of material in the Armed Forces Medical Library unless one of these ends, or another seemingly valid one, is served thereby.

In the historical department, there are various kinds of documentation other than books and journals—portraits, caricatures, autograph letters, bookplates, stamps, to name but a few—useful to research and to propaganda. Their acquisition, desirable as it is, must, with us, depend on the bounty of those of our friends whose genius and generosity are oriented in those directions.

Gifts. The oft-invoked limitations of space and personnel, wedded to our concept of function, result inevitably in the theory of selectivity being applied also to acquisitions by gift—but, happily, less rigorously. The most critical question we ask ourselves is: Is this a library we would normally turn to, if in need of this material? In general, acquisition by gift enriches us in the shape of the personal libraries of our friends (notably, in recent years, those of Drs Krumbhaar and Packard); sociological materials of medical history such as those mentioned immediately above and to be mentioned below; association items; and, occasionally, texts whose application to medical history is incidental but thought to be potentially tempting to the adventurous historian.

Coda. It is one thing to own articles of faith, of course; another, chastely to abide by them. Further, it may also be said that some degree of flexibility in the management of our human affairs is neither unheard of nor necessarily a venal sin. In the library, we are not masters (nor for a moment think of ourselves as such) but rather the gentle pastor harboring the Proverbial feeling that there must be *a* vision, however transitory and mutable, that the people may not perish.

The New History Corner

From the President of the College, and from the Librarian, the reader will already have learned of the imminent realization of some of our cherished library dreams. In the present jurisdiction, it is fitting to mention only, and briefly, the nascent history corner. Of several locations proposed for historical work and play, the one chosen is at the west end of the Norris (current periodicals) Room. A 7′ partition, diminishing disturbance from unrelated activities but preserving desirable lighting and circulation of air, will provide, on one side, shelving for periodicals, on the other, for the historical department's books. New shelving will also be installed along the south, west, and north walls. The area will accommodate comfortably, it is expected, eight readers at one time. It will be an area not for the housing of rare books (more safely maintained in the fireproof stacks) but for the use of them. The shelving in the corner, with additional shelving in the curator's office, adjacent, will accommodate, if the selection be judicious, a large part of the secondary historical material in common use and the department's special card indexes as they are compiled. The main catalogue, as our readers know, will be but a few feet away, across the main lobby. Behind the curator's office, another room will serve in time for the department's laboratory work.

In this corner, readily accessible to every user of the library, and at any hour the library is open, the confirmed or the temporary disciple of Clio Medica will have relative quiet, many of his working tools at arms' length, and sympathetic assistance awaiting his call. To Presidents Schaeffer, Miller, and, most decisively, Kern; to a host of the Fellows of the College and layman friends of the College, these disciples (including the historical department) owe and will pay the warmest tribute. Nor will they doubt that, under the equally dedicated hands of President Scheffey, adequate endowment for the historical department will follow as a matter of course from completion of the current campaign for adequate endowment of the great library as a whole.

Acquisitions

We are happy to record still another large donation of books from the library of our former president and incomparable benefactor Dr E. B. Krumbhaar. It will be recalled that these donations have been checked for duplication prior to receipt, with the result that each title represents an unquestionable addition to our resources. Though each title invites comment, limitations of space obviously dictate the reluctant use of a blanket vote of thanks and appreciation, if a brief record is to be made of a few of our other acquisitions, partly as a tribute to donors, partly for unusualness of content, partly in illustration of some aspects of the dogma on acquisitions outlined above.

Books

15th century

Guglielmo da Saliceto. Chirurgia. (Italian). Venice, Ferrariis, 16 Dec. 1491. (Klebs 485.3. No other copy in the U. S., according to Stillwell; the third of the three 15th c. editions in Italian, the collection already containing the first.)

(*bound with*)

Guido de Cauliaco (Guy de Chauliac). Chirurgia. (Italian). Venice, Quarengiis and Occimiano, 21 Aug. 1493. (Klebs 492.2. The second of the two 15th c. editions in Italian, a copy of the first being already in our collection.)

16th century

Vallambert, S. de. Cinq livres, de la maniere de nourrir et gouverner les enfans des leur naissance. Poitiers, 1565. *Gift of the Philadelphia Pediatric Society*, at the suggestion of Samuel X Radbill, M.D. (Only copy in the Philadelphia area of the first pediatric treatise in French. For a description of the book, cf. Dr Radbill's article on it in *Pediatrics*, November, 1954.)

17th century

Blasius, Gerardus. Anatome animalium. Amsterdam, Boom, 1681. ("... a valuable introduction to the history of zootomy, since most of the relevant literature published up to that time is skilfully handled by one of the best known of its exponents" (Cole). Completes our set of the three works on comparative anatomy published by this professor of medicine under his own name.)

Bulwer, John. Chironomia: or, the art of manuall rhetorique. London, Harper, sold by Twyford, 1644. *Gift of E. B. Krumbhaar, M.D.* (apart from his large donation). (Wing 5466. One of Bulwer's works entitling him to the credit of instituting instruction for deaf-mutes in England. Other publications of his are in the library.)

Ferdinandus, Epiphanius. Centum historiae, seu observationes, et casus medici. Venice, Ballionus, 1621. (An impressive volume of medical observations and histories that is said to have been highly praised by the master clinician Baglivi. The only one of the author's four published medical works in our collections.)

18th century

Bennet, Christopher. Theatrum tabidorum: or, the nature and cure of consumptions. London, for W. and J. Innys, and J. Osborn, 1720. (The library has long had the original, Latin, edition of this highly regarded work, published in 1654. It seemed fitting, 300 years later, when there is no longer a universal language, to provide ourselves with this translation into the author's and our native language.)

Desessartz, J.-C. Traité de l'education corporelle des enfans en bas âge. Paris, Herissant, 1760. (Credited with having introduced a new and more scientific view of infant feeding. Inspired, in part, by the gift of the Vallambert, this purchase signifies an historical cell that is strong and popular enough to encourage scientific feeding.)

Santa Anna, J. J. de. Elementos de cirurgia ocular. Lisbon, 1793. (The ophthalmological cell also is a strong one. This Brazilian work contains a fine engraving of an eye operation, and two plates demonstrating instruments, that are not found in the treatises on which it claims to be modeled, these being in the library.)

Sydenham, Thomas. The entire works. London, Newberry, 1769. *Gift of Mrs J. B. Tate, through David M. Davis, M.D.* (An edition of the works of the

English Rush not in the library is always welcome. This copy had a special ticket of entry in the bookplate and signature of Gen. Calvin Jones (1775–1846), one of the most prominent of the early citizens of North Carolina and Tennessee; and who, a physician, introduced the practice of vaccination into that section of our country.)

19th century

Jenner, Edward. An inquiry into the causes and effects of the variolae vaccinae. 2d ed. London, 1800. (This rounds out our set of the first three London editions.)

Tensas, Madison, M.D., *pseud.* Odd leaves from the life of a Louisiana "swamp doctor". Phila. Peterson, 1858(?). (This rare and engaging gem of American humor, apparently little known to medical historians, came to our attention through a research study, undertaken by John Q. Anderson, Ph.D., whose primary aim was to identify the pseudonymous author. Through our collection of early medical school catalogues, it was possible to confirm Dr Anderson's thesis that the author was Henry Clay Lewis, M.D.; further, to make it clear that the medical faculty and curriculum described so entertainingly by the author were those of the Louisville Medical Institute, at a time when the faculty included such illustrious figures as Daniel Drake, Samuel D. Gross, and Charles Caldwell. Though the book was published in Philadelphia in a number of editions, this is only the third copy in the area, and the only one in a medical library.) (See Anderson, J. Q., "Henry Clay Lewis, Alias 'Madison Tensas, M.D., the Louisiana Swamp Doctor'", Bull. M. Library A. **43:** 58–73, (Jan.) 1955.)

Pestschutzbriefe und Essbilder

Continuing his welcome additions to our collection of materials illustrating practices in folk-medicine, *Dr. J. Monroe Thorington*, a member, with others named here, of our corps d'élite, donated a series of *Pestschutzbriefe*—small printed "letters" containing a text and illustrations of religious character that the peoples of Austria and Switzerland carried with them as a prophylactic against the plague and other diseases; and five *Essbilder* of the 18th century. These latter are small woodcuts of religious subjects which the pious ate, again as a prophylactic. Accompanying the *Essbilder* was a 1953 *Alter BauernKalendar*, whose small illustrations of similar character are said to be used for the same purpose today.

Lantern Slides

Our Packard Collection of lantern slides on medico-historical subjects is now notably supported by a large additional collection donated by another good Fellow and friend, *Dr William G. Leaman, Jr.* Both collections are, of course, available for loan.

Autograph Letters

1.) *Dr Krumbhaar* has donated another file of interesting letters received by him from various distinguished correspondents over a number of years. 2) *Dr Burton Chance*, among other characteristically understanding gifts, donated letters from E. Treacher Collins, Harvey Cushing, W. Lang, and two former presidents of the College, Hobart Hare and W. W. Keen. 3) Five fine letters of the late Dr Maude E. Abbott, of Montreal, were presented by our Fellow *Dr Rachel Ash.* Dr Abbott, who visited the library several times, will be recalled for her "Garrison-Morton Classic" on congenital cardiac disease, and for her early bibliography of Osler's writings. 4) *Dr A. E. Taft* pleased us with her gift of letters, photographs, and a Christmas card received by her from the internationally known Dutch anatomist C. U. Ariëns Kappers, whose visit to the library some years ago is also well remembered. 5) An interesting letter written by Samuel Hahnemann, with another letter, written by his wife, was gratefully received from our friends the *Messrs George and Ernest Allen*, as gift of *Mrs Joseph H. Beattie.* 6) To our Fellow *Dr Samuel B. Hadden*, there is indebtedness for a letter of high personal interest written by Joseph Priestley, the great English theologian and scientist, to a Pennsylvania friend, John Vaughan, in 1793, shortly before Priestley crossed the ocean to join his sons in this country. 7) There closes this section a letter which is of no particular importance unless it be thought important to stop briefly now and then and examine a pure example of the humanitarianism implicit in medicine. The writer, Dr J. P. McGee, of Trenton, Tenn., was graduated from the Jefferson Medical College in 1861, and could therefore have been but a

little older than the 22 year old soldier and friend whose last days he describes in this letter to the young man's sister. The kind donor of the letter was *Mrs John Q. Anderson.*

Pulaski, Tenn.
31 Jan'y 1865

Mrs Bills,

Your Bro. Luther was brought to one of my Hospts on the night of the 24 Dec'r (by Dr. Alex. Hamilton of Trenton) with his right Thigh badly shattered. He was wheeling when struck. The ball struck near the middle of the Thigh on its outer side—ranged downwards and inwards *through* the knee joint, comminuting about 4 or 5 inches of the lower part of the bone and opening the joint.

During all of that night and the next day he was suffering such depression from "Shock" that it was not prudent to operate until the morning of the 26th, when I, assisted by Surgn Abernathy, amputated at the middle third. He lost but little blood in the operation (a good deal on the field) but, notwithstanding the free use of stimulants, essence of beef, and every means that could be brought to bear, he sunk gradually, but steadily until the night of the 28th when he sunk to rest calmly and peacefully. After the first night he suffered very little, for so severe a wound.

I was fortunate enough to procure a nice cotton mattrass & a pillow for him and made him as comfortable as it was possible to do.

I assure you that every possible attention was bestowed, both by the surgns and nurses; that nothing was left undone that would benefit or comfort him during the few days he lived.

No duty of my life has been more unpleasant than this, to communicate to you this sad intelligence. He was truly a noble jewel to the army and Society, as well as to you, and the balance of his bereft relations. And deeply & truly do I, with you, mourn his untimely fall.

Very truly,
Your Friend
J. P. McGee

Exhibits

Major exhibits were devoted to commemorating the 400th anniversary of the death of Girolamo Fracastoro; the 125th anniversary of the birth of S. Weir Mitchell; and the 100th anniversary of the birth of Paul Ehrlich.

Curatorial Doings

The Curator had, in the January, 1954, issue of the *Journal of the History of Medicine*, a report ("Benjamin Waterhouse's Manuscript Notes on the Lectures of John Hunter, 1777–78") on an interesting manuscript in our collections; prepared a report (unpublished) on the First International Congress on Medical Librarianship for the Philadelphia Regional Group of the Medical Library Association; contributed a book review to the *Bulletin of the Medical Library Association.* His introductory address at the International Congress was recently published in the *Proceedings* of the Congress. He served as chairman of the nominating committee of the Friends of the Armed Forces Medical Library. As mentioned elsewhere, for four of the months covered by this report he was on a leave of absence graciously maneuvered by Dr Rhoads, the kindly chairman of the Library Committee. Relinquishing the editorship of the *Transactions & Studies* with the issue in which this report appears, the Curator looks forward to repaying this kindness, and many others, by closer dedication to the interests of the young historical department.

W. B. McD., 2d

STATISTICAL SUMMARY

Inventory

	1954	*1953*
Total number of accessioned[1] items	186,852	183,991
	1954	*1953*
Incunabula	419	417
Manuscripts (including a few typescripts)	796	787
General	181,319	178,610
Accessioned pamphlets	4,320	4,177
	186,852	183,991

STATISTICAL SUMMARY—*Continued*

	1954	1953
Total number of unaccessioned[1] items	325,610	324,312
	1954	*1953*
Reports	28,015	27,568
Periodicals "reserve"[2]	9,332	9,002
Theses and Dissertations	57,166	56,832
Pamphlets and reprints	231,097	230,910
	325,610	324,312
Total number of current periodical publications and serials regularly received	1,930	1,739
Portraits[3]	91,297	85,836

Distribution of This Material

	Accessioned Items	*Unaccessioned Items*
General Library (including the Lewis Library)	182,490	325,606
On permanent deposit:		
Gross Library	3,945	4
Parry Library of the Obstetrical Society of Philadelphia	217	0
Mütter Museum[4]	200	0
	186,852	325,610

Current Serials[5]

	Purchased	*Exchange or Gratis*	*Total*
U. S. A.	344	413	757
Western European Continent	609	77	686
Latin America and West Indies	59	112	171
United Kingdon and Eire	125	28	153
Canada	9	26	35
Eastern European Continent	18	5	23
Asia (including Japan)	17	52	69
Africa	4	11	15
Pacific (including Australasia)	4	17	21
Grand Total: 1954	1,189	741	1,930
Grand Total: 1953	1,119	620	1,739

New titles: A total of 121 serials was added in 1953–54. Sixty-three of these were purchased; fifty-eight received in exchange or gratis. Sixty-two began with volume 1.

Separate Issues received, checked-in on the cards, and shelved totaled 15,886. In addition, thousands of duplicate issues were received, as usual; 330 of these were retained for our 'reserve' files, no attempt being made to count those held merely for exchange or other use.

Visitors in the Norris Room for the year totaled 4,457.

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[1] Accessioned items in this library comprise the total number of bound volumes and such unbound pamphlets as have been catalogued as separate bibliographical units regardless of their size.

There remain many thousands of unaccessioned pamphlets awaiting accessioning and cataloguing. A true quantitative and qualitative picture of the library's holdings can not be presented until this wealth of neglected material has been processed and duly registered in our 'accessioned', or 'volume', count.

[2] More-or-less complete duplicate volumes of periodicals.

[3] Including 122 oil, and 427 other, framed portraits in the care of the Committee on College Collections. The count of portraits represents the number of entries on the cards in the portrait catalogue. The entries represent, in turn, both loose portraits and those in books, many of them, of course, being merely different reproductions of a single original.

[4] The books of the Mütter Museum are not permitted to be removed from the College building.

[5] For the first time serials other than periodicals have been included in this tabulation. There are 200 serials in this year's count which would not have been included previously.

Readers' Use of the Library

Library Hours. The library was open, during the academic year, from 9:30 to 9:30 on Mondays and Wednesdays; from 9:30 to 5:30 on the other weekdays. During the latter half of June, in July, August, and the first half of September the Library was open from 1 to 9:30 on Tuesdays; from 9 to 5 on the other weekdays, except Saturdays, when it was closed. The following legal holidays were observed: Thanksgiving (beginning at 5:30 on the preceding evening), Christmas and New Year's (and a half day preceding each), Memorial, Independence, and Labor Days. The library was closed the first week in August for repairs.

Visitors:

	Totals	*Reading Room*	*Periodicals Room*
1954:	12,973	8,516	4,457
1953:	13,975	9,277	4,698

Circulation:

	Totals	*Intra-mural*[6]	*Extra-mural*	*Books*	*Journals*
1954:	41,084	30,866	10,218	8,299	32,785
1953:	47,788	39,395	8,393	10,558	37,230

[6] The number of volumes "consulted in the library" includes only those supplied on demand. Readers have access to the bound volumes of periodicals and reference works kept on the shelves in the Reading Room; the Fellows, and occasionally others, by special permission, have access to the book-stacks. There are, therefore, many volumes consulted of which no accurate record can be kept.

Inter-library loans: The library sent 3,462 (1953: 2,616) volumes on inter-library loans to 126 (1953: 127) libraries in 28 (1953: 29) States and 4 Provinces and has borrowed 2 (1953: 2) volumes from 2 (1953: 2) libraries.

Photostats: 3,714 photostatic prints were furnished on request (1953: 3,438).

Acquisitions and Accessions

Accessioned Acquisitions:

1954: 2,800 volumes (1,737 by purchase; 903 by gift; 160 by exchange). (*Books:* 867, *Periodicals:* 1,933); 143 pamphlets.

1953: 2,525 volumes (1,732 by purchase; 613 by gift; 180 by exchange). (*Books:* 952; *Periodicals:* 1,573); 90 pamphlets.

Non-accessioned Acquisitions[7]*:*

1954: 447 Reports (1953: 503).
334 Theses (1953: 165).
139 Miscellaneous items (1953: 160).

Donations

The donors for the past year number 230 (1953: 318). The library is indebted for large gifts of books, pamphlets, and unbound periodicals to the following donors: Donner Foundation; Hahnemann Medical College Library; Lea & Febiger; J. B. Lippincott Co.; W. B. Saunders Co.; Smith, Kline & French Laboratories; and Wyeth, Inc.

Various publishing houses, among the large group of corporate donors, have presented volumes as follows: Blakiston Co., 14; F. A. Davis Co., 3; Lea & Febiger, 17; J. B. Lippincott Co., 36; W. B. Saunders Co., 62.

Other individual donors were as follows: Mrs J. Q. Anderson; Drs R. Archila, J. H. Arnett, M. B. Asbell, E. Atlee; Mrs J. H. Beattie through G. Allen; Drs W. R. Bett, W. C. Bird, S. Bishop, W. N. Bradley, J. Broadman; Prof. L. H. Butterfield; Drs J. J. Byrne, F. Callomon, B. Chance, J. M. Deaver, C. F. Enloe, S. Garcia-Vicente, S. B. Hadden, P. Hartman, E. Hess, A. C. Ivy, C. Jackson, C. L. Jackson, R. A. Kern, J. V. Klauder, E. B. Krumbhaar, H. Kuhlenbeck, W. R. Lang; Mrs I. Langman; Dr W. G. Leaman, Jr.; Mr G. Legman; Drs W. T. Longcope, E. Lundsgaard; W. B. McDaniel, 2d; Drs D. Macfarlan, S. Misra, J. Nasio, W. Overholser; Packard Estate Books; Drs K. E. Paschkis, M. Pfeiffer; Prof. Emeritus M. H. Phillips; Drs S. X Radbill, M. E. Sano, T. G. Schnabel; Miss E. E. Schramm; Dr D. Schullian; Drs L. L. Schwartz, W. B. Shelley; Prof. R. H. Shryock; Mrs W. A. Smith; S. M. Spencer; Drs J. C. Stolz, S. Tarachow, J. M. Thorington, E. R. Trethewie; Mrs R. B. Twining; Dr J. R. Twiss; E. Wolf, 2nd; Drs H. B. Wood, H. C. Wood, Jr., W. Zentmayer.

Exchanges

The *Transactions & Studies* was sent, either in exchange or as gift, to 267 organizations.

The library received a number of journal issues through the Medical Library Association Exchange and USBE and supplied duplicate journals to other libraries through MLA, USBE, and others.

Theses and dissertations to the number of 334 have been received on exchange from the following European schools of medicine: Universities of Basel, Bern, Copenhagen, Erlangen, Geneva, Jena, Lausanne, Leiden, Louvain, Tübingen.

[7] As usual, not all the pamphlets, theses, and numbers of various journals listed as received had been checked for keeping or discard at the close of the library year.

Work of the Cataloguers

	1954	*1953*
Accessioned items catalogued or recatalogued	815	952
Unaccessioned items and Fellows' reprints catalogued by author or by author and subject	37	186

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Annual Report of the Committee on the Mütter Museum and College Collections*

The Museum

The year 1954 has been a busy one in the Mütter Museum. Visitors from all parts of the United States and from foreign shores again stopped in to see its many exhibits and to study some of its specimens. The Museum was host to classes from the Franklin School of Arts and Sciences, to student nurses from the Fitzgerald Mercy Hospital and the Lankenau Hospital, to fifty pupils from the Bok Vocational School, to forty-six students from the Woman's Medical College and to thirty biology students from the Immaculata College. Special arrangements were made for a conducted evening tour of the Museum for the Osler Club from the School of Medicine of the University of Pennsylvania. In all, there were more than 1800 visitors during the year.

Special exhibits from the Museum collection were displayed on the six nights when special lectures were given on Medical History.

Dr. Oscar V. Batson, Professor of Anatomy at the Graduate School of Medicine of the University of Pennsylvania, arranged with Dr. Mary Elmore Sauer of the University of Texas, for the loan of her special exhibit of *Anatomists on Postage Stamps*, which was displayed for a time in a case on the upper floor of the College.

Nineteen more articles on Museum subjects appeared in *Philadelphia Medicine* bringing the total to date to sixty-two. Mr. Joseph Sunner, from the Presbyterian Hospital, has already taken many photographs to illustrate the articles.

The Sixty-seventh Thomas Dent Mütter Lecture was given December 1, 1954 by Seymour S. Cohen, Ph.D., Professor of Physiological Chemistry at the School of Medicine, University of Pennsylvania, and also Professor of Physiological Chemistry in Pediatrics at the Children's Hospital of Philadelphia. The title of the lecture was *The Chemical Pathology of the Virus-infected Cell*. The lecture will be found in the February, 1955, issue of the *Transactions & Studies*.

While the majority of the gifts received were placed in College Collections, the Museum can boast of a cast of a 4000-year-old clay Sumerian Medical Tablet translated, in 1954, from the original in the University of Pennsylvania by Dr. Samuel Noah Kramer of the University Museum and Dr. Martin Levy, teacher of chemistry at Pennsylvania State College. It was presented by *Dr. Douglas Macfarlan*.

A variety of instruments, of which the Museum has no duplicates, were given by *Dr. Alexander H. O'Neal*. Among these are a Dialvue thermometer, a Janeway sphygmomanometer, Dr. Rogers' Tycos sphygmomanometer, two metal finger splints, a set of Jarvis fracture treatment instruments, an O'Dwyer intubation set, a set of dissecting instruments used by four generations of physicians, several hypodermic syringes, an Ultzmann urethral syringe, a Gersler-Lowman bone plate holder, a stethoscope used in obstetrics, a case of surgical needles exhibited at the St. Louis Exposition in 1900, Gwathmey's early model of a nitro-oxide set for prolonged anesthesia, a case of hard rubber nose and throat instruments and a nasal aspirator.

Dr. Stirling W. Moorhead presented the Museum with a variety of urethral instruments consisting of five urethrotomes, two stone searchers, three urethral irrigators, Freudenberg's modification of Bottini's cautery prostatic incisor, dated 1897, the *Diviseur Vésical Gradué* of Fernand Cathelin and *Le Séparateur* of Georges Luys.

Five bone plates, used by Dr. Wayne Babcock fifty years ago were presented by *Dr. Milton F. Percival* and *Dr. William N. Bradley* presented a small catheter.

Mrs. Ella N. Wade was reappointed curator

* 1 December 1953–30 November 1954.

and clerk-technician for the year 1953–54, and was in attendance Mondays through Fridays from 9.30 to 1 and from 2 to 4.30, and on Stated Meeting Nights of the College until 8.30 P.M.

The College Collections

As usual, the College Collections were augmented by a great number of interesting gifts from friends of the College and Museum. *Dr. J. Monroe Thorington* presented fertility and virility charms mounted in silver, three glass ophthalmic drug retorts, two wool tests devised by Dr. William Thomson for color-blindness, a model of a human eye used in office demonstration by Dr. James Thorington, American Ambulance insignia from World War I, a brass scarificator from Vienna, ca. 1800, and the Schabmadonnen—eight plaster figures—dating from 1750 to 1800, from Einsiedeln, Switzerland.

The *Friends Historical Society* presented the plaster cast of the head of Dr. Fothergill's gold-headed cane, engraved, like the original gold-headed cane, with the names of its various owners.

Dr. Burton Chance, who never forgets the College when he finds interesting material, donated nineteen ophthalmic instruments formerly belonging to Dr. Paul Sartain, Dr. William Thomson's wool test for color-blindness, a small microscope formerly belonging to Dr. William Thomson, two caustic holders for copper and alum used on the eye in cases of trachoma and eighteen aids to the diagnosis and measurement of refraction and muscle action.

Dr. Douglas Macfarlan also presented a small microscope that formerly belonged to Dr. Samuel H. Worcester who practiced in Salem, Massachusetts.

Dr. William N. Bradley, almost a weekly visitor to the Museum and College, presented a beautiful colored photograph of the oil portrait by Franklin Watkins, of Dr. Edward Strecker.

Dr. Edward F. Corson, who usually adds to the medal collection, this year surprised the College with the gift of a small pipe that once belonged to Dr. Joseph Leidy.

Two new donors are represented this year, namely *Dr. John Peoples*, who gave a wooden plaque containing the seal of the Medico-Chirurgical College and *Dr. William D. Griggs*, who presented a medal of Benjamin Rush.

Dr. George E. Pfahler replaced the original plaster bust of Professor Roentgen that he presented in 1945, with a handsome bronze copy.

The oil portraits of Dr. James Hutchinson, Dr. John Morgan, Dr. John Carson, Dr. William Cullen, Dr. Roland Curtin and the self-portrait of an insane patient from the Philadelphia Hospital, were restored by Mr. Frank Ireland. The regular yearly repair of a few portraits is putting the portrait collection in excellent condition.

Two portraits of Dr. S. Weir Mitchell, one by Vonnoh and the other by Dvorak, were loaned to the Free Library for exhibit at the 125th anniversary of the birth of Dr. Mitchell.

At the request of Dr. Samuel X Radbill, the Osler and Welch medals deposited in the College by the Section on Medical History, were loaned to the Historical Medical Library of Yale University for a special exhibit.

Mrs. Wade was reappointed custodian of College Collections for the year 1953–54.

R. Philip Custer
Chairman

Annual Reports of the Sections*

General Medicine

There were, as usual, four presentations at each of the six meetings of the Section. Abstracts of thirteen will be found in the *Transactions & Studies*. Of the seventy-seven authors and discussers, 41 were Fellows, and 36, guests. The Section had one hundred and fifty members, with an average attendance of 32.6%.

Perry S. Mac Neal
Clerk

Medical History

One of the important functions of the Section this year was to stimulate further interest of the five medical schools of our city in the history of medicine.

The same fall lectures as in previous years were given to the medical students by Prof. Richard H. Shryock and Doctor Owsei Temkin. They were fairly well attended. They were also attended by representatives of the medical schools who will take part in the seminars this coming spring.

In the spring of 1955 eight seminars will be given by Doctors Shryock and Temkin on methods of teaching medical history. These seminars are open to all Fellows of the College and are to be given under the combined auspices of the Section and the medical schools of Philadelphia. The basic principle of the seminars is to cultivate the interest of those who would like to give introductory lectures in medical history in their respective medical schools. It is hoped that such an interest will appeal to more medical students and thus give "birth" to medical historians of tomorrow.

The Section this year offered an award of $100 for the best essay on a medico-historical subject submitted by a student of any one of the medical schools of Philadelphia. The prize was awarded to Irwin Brody, of the University of Pennsylvania, and honorable mention went to David C. Schechter, of Jefferson Medical College. Mr. Brody's title was "The School of Medicine at Jundishapur: the Birthplace of Arabic Medicine"; and Mr. Schechter's title was "The Battle of the Ten Plagues, or the Birth of Biological Warfare". It is expected that Mr. Brody's paper will be published in the *Transactions & Studies* of the College. The Section has authorized a similar prize for 1955.

Four meetings of the Section were held during 1954, the last one in conjunction with the Philadelphia Neurological Society. The papers on S. Weir Mitchell read at that meeting by Doctor I. S. Wechsler and Prof. Ernest Earnest will be found in the February, 1955, number of the *Transactions & Studies*.

In May, 1954, Doctor R. J. Hunter represented the Section at the Annual Meeting of the American Association of the History of Medicine in New Haven, Conn. Doctor Samuel X Radbill represented the Section at the 14th International Congress of the History of Medicine in Rome in September, 1954, together with Doctor Maurice S. Jacobs.

Nicholas Padis
Clerk

Ophthalmology

During the calendar year, the Section held seven regular and one special scientific sessions and has held three executive sessions.

The Section is made up of 65 Fellows. The average attendance of the meetings was 26 Fellows and 69 guests, making an average total of 95. Small dinners were held at the Orpheus Club before each of the meetings where guest speakers were heard, and a dinner attended by 69 Fellows and guests was held at the Warwick

* The programs of the Sections will be found—under the heading, "Transactions of the Sections"—in the August, 1954, issue and this issue (April, 1955) of the *Transactions & Studies*. The names of their officers in 1954 appeared—under the heading, "Officers, Committees, Sections . . ."—in the April issue of that year; current officers are listed under the same heading in the present issue.

Hotel preceding the de Schweinitz Lecture. The expenses for these dinners were borne by the Fellows who participated and not by the Section.

Contributions to the College Building Fund were made as follows: $1,000 in March and $500 in December, making a total of $1,500 for the year.

The annual award of $50 in honor of Dr. William Zentmayer was given to Drs. H. P. and Marie W. Kirber for their paper given before the Section in December, 1953.

William E. Krewson, 3rd
Clerk

Otolaryngology

During 1954 six meetings of the Section were held at the College. The March meeting was held jointly with the Section on Otolaryngology of the New York Academy of Medicine. Twenty-seven members of the Academy came to Philadelphia for the meeting.

Papers were presented during the year by 15 members of the Section and 9 guests. There was an average attendance of 29 members and 31 guests, an average total of 60.

The present membership of the Section consists of 59 Active Fellows and 5 Honorary Fellows. During 1954, one new Fellow, Dr. Thomas McGlade, became a member of the Section. Two Honorary Fellows, Drs. Ralph Butler and George B. Wood, were lost by death.

Philip A. Marden
Clerk

Public Health, Preventive and Industrial Medicine

The Section, with a membership of 53, held one meeting during the year, which was attended by approximately 65 members and guests.

The subject was "The New Education Program at Western Reserve University", the principal speaker being John L. Caughey, Jr., M.D. The invited discussers were Charles L. Brown, M.D., John McK. Mitchell, M.D., J. Earl Thomas, M.D., W. Edward Chamberlain, M.D., and Ann Holsinger.

Dr. Caughey discussed in some detail the new educational program for medical students which had been in existence for the past two years. This program includes integration of basic and clinical sciences. The medical student has personal contact with patients during his entire four year curriculum. During the first two years attention is focused upon the relationship between the patient and basic sciences in medicine. Treatment of disease is introduced in the third and fourth years. Dr. Caughey stressed the following points: 1) There is a definite need for a study of teaching of medical students. Are our present methods the most efficient possible? 2) There is at present a change in the status of the teacher of medical students. 3) Are research scientists needed for the elementary teaching of medical students? 4) Would it not be wise to cross departmental lines and so produce a "scientific general practitioner"? 5) Faculties need attention focused on medical teaching in school and not merely in hospitals and graduate courses. 6) There is no substitute for discussion and for time.

Discussion was opened by *Dr. Brown*, who emphasized the need to integrate a coordinated pre-clinical and clinical phase of medical education. There was some discussion of the relative expense of part and full-time medical teachers. *Dr. Mitchell*, discussing the problem from the standpoint of the Curriculum Committee, stressed the importance of thorough discussion of all forms of teaching. *Dr. Thomas* discussed the problem from the standpoint of the preclinical teacher. He believed that not enough basic science is being taught at present —that the Western Reserve plan would work with good teachers, and that present day medical students need not be confused. *Dr. Chamberlain*, representing the viewpoint of the clinical teacher, was very enthusiastic about the Western Reserve plan. He stressed that there is always room for improvement in teaching methods and he was delighted that Western Reserve "threw the book away". Miss Holsinger, senior student at Woman's Medical College, raised these questions: 1)

What should pre-medical students study? 2) How should medical and pre-medical students be selected? 3) How important is time spent in lectures? She made the point that students are interested in experience rather than in didactic teaching.

In closing the discussion, *Dr. Caughey* remarked that "there is little place in the medical school for people doing *only* research". The method of selection of students at Western Reserve has not been changed. There is no over-supply of able people applying for admission. During the second year groups of four students work up patients. This is better than correlation conferences. The Western Reserve Plan is in favor of less "cook-book laboratory work". Examination grades are deliberately devalued; students cannot retain information learned just for examination, as has been confirmed by repeating the same examination one year later. It is important to stop the anxiety of the faculty as well as that of the students. In summary, the undergraduate students are treated almost like graduate students, and great stress is laid on indoctrination with the proper attitude toward medicine.

ROBERT V. COHEN
Clerk

Memoir of William Henry Donner (1864–1953)*

By T. GRIER MILLER

WILLIAM HENRY DONNER, an Honorary Associate Fellow of this College, died in Montreal on November 3, 1953. He was of German-English descent. His father, as a child of eight years, came to America from Stuttgart, Germany and grew up in Hope, Indiana. There he entered into the jewelry business, in which he continued to function for fifty years. William Donner's mother was Mary Jane Johnson. She was one of the early crusaders for prohibition in this country and lived to the age of ninety-one. Both parents originally were Moravians, later, on moving to Columbus, Indiana, becoming members of the Presbyterian Church.

William Donner was born in Columbus on May 21, 1864. He was in his ninetieth year at the time of his death. Little is known of his childhood, but he often spoke with affection of his mother, of her wisdom and her influence on his life. In 1882 he attended Hanover College, Indiana. Although his youthful ambition had been to become an engineer, he soon became involved in business affairs. His administrative genius was such that at the age of eighteen he took over, for his father, the management of a local milling company. At the age of thirty he left Columbus to establish in Anderson, Indiana, a tin plate business organization. In the prosecution of his success in that industry, he founded the town of Monessen. In 1899 he went into the steel business with the Mellon and Frick interests and founded the town of Donora, where he constructed a rod, wire and nail plant. Subsequently he became, in turn, president of the Union Steel Company, the Cambria Steel Company, the Pennsylvania Steel Company and the Donner Steel Company. Also, he became a director of several large banking institutions.

In 1929, Mr. Donner's son, Joseph W. Donner, died of lung cancer. The father then retired from active business and returned to Philadelphia, where previously he had lived (from 1914 to 1916). Subsequently his interests were largely of a philanthropic nature. With an initial fund of $2,000,000 he established what is now "The Donner Foundation". Its original objectives were to increase interest in cancer research, to develop new theories, to broaden the viewpoint of investigators and to increase cooperation among the workers in that field throughout the world. Its functions have since been broadened to cover many other philanthropic and educational activities. Later he contributed more than $1,500,000 to Hanover College. This led to donations by others and eventually made possible the construction of five of that College's ten new buildings and permitted the improving and beautification of its campus. In Columbus he established a 42-acre park in memory of his mother. In addition, he gave to that city $400,000 for the creation of a center and swimming pool for the free use of its children; $100,000 for a church house to be used for youth activities and recreation, this in memory of his father and mother, and $65,000 for a hospital radiological department.

In 1937, Mr. Donner transferred his citizenship to Switzerland where, in Montreux, he subsequently purchased and maintained a home, but he continued to spend some time in Philadelphia, Bermuda and Montreal. Donations to charity, medical science, research in medicine and education, largely through the Foundation, were continued. In 1943, the

* Prepared, and published, at the request of the Council of the College of Physicians of Philadelphia. Read before the College, 6 October 1954.

Foundation established a $400,000 fund, known as the "Donner Fund for Needy Patients", the income to be expended through the Hospital of the University of Pennsylvania for special facilities to charity patients, for assistance in clinical research and for experiments in hospital administration. Eventually this fund aided in the establishment of a full-time department of psychiatry in that hospital and made available $300,000 for the erection of a new building to house a modern kitchen, a dining room and a medical library. Even before that time the Foundation had contributed $200,000 for the equipment of the radiological department of the same institution. Also, it financed the construction of the Donner Laboratory of Medical Physics at the University of California, at Berkeley, and, at Mr. Donner's suggestion, initiated and sponsored in Philadelphia a series of clinics for the early detection of cancer in women.

Eventually Mr. Donner established in Canada another foundation for charitable, educational and medical purposes. Through this agency, he made possible at McGill University the construction of a building for research in medicine and biophysics and provided funds for the operation of that University's Neurological Institute and for a research fellowship.

Before Mr. Donner's death, his American Foundation agreed, on a conditional basis, to make a donation of $100,000 to our current College campaign for a building fund. This condition, like that of most of its other gifts, involved the acquisition of other bequests from members and friends of the institution. Thus, it has served as a stimulus to all of us to strive for our ultimate goal of a new library building, and I am privileged to announce this generous gift to-night.

On the day before his death, Mr. Donner was nominated as an Honorary Citizen of Montreux and, in recognition of his generosity in the establishment of a playground for its children, was awarded a Certificate of Honor by that municipality.

This outline of Mr. Donner's benefactions is presented to indicate his intense interest in the advancement of medical science, the amelioration of human suffering and the promotion of social welfare. Incidentally, it illustrates his devotion to his family and friends; also, his regard for the localities in which he had lived, received his education and profited by his business associations.

Mr. Donner had much personal charm. He was a quiet, unassuming and gracious gentleman. He was tolerant of others' opinions, but was not easily influenced. He had his own ideas and was determined about matters on which he had deep convictions. He was generous, but shrewd and cautious. He had an original mind and initiated many important procedures in the steel industry. He was admitted to Honorary Associate Fellowship in our College, however, because of his interest in the art and science of medicine and in humanity, and he will be remembered longest for the contributions he made in support of these objectives.

Memoir of Balduin Lucké (1889–1954)*

By EDWARD B. KRUMBHAAR

DOCTOR LUCKÉ was born on November 3, 1889 at Oedinghausen, Hesse, Germany and died at his home in Bryn Mawr on April 26, 1954. He had come to the United States in 1906, graduating at the Medico-Chirurgical College of Philadelphia in 1912, and being made a Doctor of Public Health by the University of Pennsylvania (1916). He was an intern at the Philadelphia General Hospital from 1912 to 1914, and in 1914 entered the Department of Pathology of the University of Pennsylvania. There he continued until his death, first as an assistant instructor and rising through the various grades to become a professor in 1932 and chairman of the department in 1947.

In World War I, he was assigned to the Laboratory at Camp Zachary Taylor with Major Allen J. Smith, under whom he had already served at the University. At Camp Taylor, when autopsies could be performed almost ad lib., he took advantage of the great opportunity to study the influenza pandemic, both in the varied lesions produced in the lungs and to search for the causes of its high pandemic mortality. Human virology being still in its infancy, he was limited to bacterial studies, finding the Hemophilus influenzae, then thought by many to be the primary cause, to be replaced by streptococci, pneumococci and staphylococci as the pandemic progressed. This readily fitted into the view that resistance was so lowered that the patient easily succumbed to secondary invaders. Only with the later discovery of a filtrable virus (1934) did the true cause of the disease become evident, and H. influenzae to a certain extent a misnomer.

Back home as a senior assistant to Dr. Allen Smith for a number of years, Dr. Lucké continued to gain experience in gross and microscopic pathologic anatomy, and in the performance of autopsies. The results of this training are especially apparent in most of the subjects of his earlier published work, starting with a clinico-pathological study of tabes dorsalis (1916), through studies of the histologic changes found in organs after various poisons, the cytology of pleural exudates, aneurysms, cerebral lesions, sarcoma in a goldfish skin (1922), chronic nephritis, liver lesions after anesthesia, lesions of the diaphragm, and so on. In this period, too, is found his apparently only published translation (1923, with Morton McCutcheon), Schroeder's *Introduction to the Histology and Histopathology of the Nervous System* (1920).

Gradually, however, his interests were changing to the study of properties of living cells, usually under conditions experimentally produced. Here, both Dr. M. H. Jacobs at the University and the Marine Biological Laboratory at Wood's Hole, where he soon acquired a small house, influenced him powerfully. In the summer, studies were mostly on cell permeability and osmosis, the eggs of the common sea-urchin being used as efficient osmometers; for problems of surface tension of cells, phagocytosis, agglutination, opsonins and the like, he combined with colleagues at the University.

Observation of an adenocarcinoma in a kidney of the leopard frog (Rana pipiens) led to an extended study of neoplasia in cold-blooded animals, both occurring spontaneously and produced experimentally. Knowledge gained from the earlier studies just mentioned proved most useful. His demonstration that the frog tumor was due to a filter-passing virus was an important contribution to the virus theory of tumor formation; it was, as far as I know, the first virus tumor to be observed in a cold-blooded animal. The frog tumor was found to occur frequently, to be readily transplantable, and conveniently to grow in a readily observable

* Prepared, and published, at the request of the Council of the College of Physicians of Philadelphia. Read before the College, 1 December 1954.

place (anterior chamber of the eye). Here it changed its structure according to its milieu, and its speed of growth according to the surrounding temperature. In still other ways the tumor cells obeyed the general laws of cell growth much as do normal cells. When the studies were extended to other cold-blooded animals—fish, reptiles, amphibia—the phenomena elicited could frequently be fitted into orderly laws. This was especially pleasing to Dr. Lucké's orderly mind, which was by nature averse to concepts of lawless growth. After the interruptions of World War II, he returned to his cancer studies, his work with A. K. Parpart on "Osmotic Properties and Permeability of Cancer Cells" being published only 4 months before his death, and another on "Ascites Tumors" (with Mary Berwick) appearing posthumously last August. In all, more than 30 original studies on neoplasia had appeared in the course of 20 years. He can justly be regarded as the leading authority on tumors in cold-blooded animals.

Dr. Lucké always supported the point of view that "pathology", interpreted as the study of the changes produced by disease, left but little that was not germane to the subject, and ipso facto often overlapped fields being covered in related medical school departments. Only "clinical pathology," more a part of clinical diagnosis than of academic pathology, was excluded by him and he accepted no responsibility for the supervision or teaching of this questionably named field.

Dr. Lucké exhibited to an unusual degree an efficient combination of scientific endeavor and executive capacity. He was a good lecturer, clear and forceful; not hesitating, where he thought it helpful, to make more categorical statements than do most lecturers. Beneath a determined exterior, a sensitive nature led him in discussions or interdepartmental conferences to keep his remarks strictly within his own province, but woe betide the unwary colleague in another field who ventured to criticize observations within that province! In the laboratory classroom, he gave his time mostly to the brighter students, for the duller or uninterested, he begrudged the time taken from his personal research work.

The military side of medicine always appealed to Dr. Lucké. He held a commission in both World Wars and after the first of these entered the Medical Reserve Corps, in which he stayed from 1919 till his death in 1954. In World War II he was attached to the Army Institute of Pathology and, as its Deputy Director, guided many measures of importance to the welfare of the Army, as well as often contributing to the essential scientific knowledge that led to their adoption. With an unequalled opportunity to study histories and tissues of many cases of epidemic hepatitis occurring in our soldiers all over the world, he worked out a clear picture of the sequence of the changes in the liver, often with complete restitution to normal (elicited from recovered cases dying from unrelated causes). The fulminating type, which appeared as the epidemic progressed, he studied in the same way, recognizing it as one type of acute yellow atrophy, just as he regarded the more benign variety as the epidemic form of "acute catarrhal jaundice." His two long publications are recognized as the standard articles on the subject. Out of this period, too, came his studies of the kidney in a number of conditions, such as crush injuries, extensive burns, incompatible transfusions, toxemia of pregnancy, blackwater fever, and lesions from various drugs and poisons. The frequent finding of a prominent degeneration in the lower part of the nephron led to his establishing a new pathological group—lower nephron nephrosis. Some pathologists, to be sure, have objected to the term, finding lesions also in the upper nephron but when can a name be expected to cover all details of a picture? His generalization, with the limitations mostly indicated in his own article, still serves a useful purpose.

Dr. Lucké was elected a Fellow of this College on October 5, 1921. He was a loyal supporter of its varied interests and contributed personally to its present financial efforts. He was a regular user of the library, whose value he thoroughly appreciated. He attended its

meetings on suitable occasions, but was more intimately concerned for many years with the affairs of the Pathological Society of Philadelphia, which is the practical equivalent of a pathological section of the College. He had been President of the Society (1930–1931) and also of the Philadelphia Physiological Society (1934–1936). He belonged to the leading pathological and biological societies of the country and had been president of several. He was active in the American Society for Cancer Research, and served on its editorial boards for several years. He was also a member of the Association of American Physicians, which includes but few pathologists. He was an Honorary Consultant of the Army Medical Library and to the Armed Forces Institute of Pathology, also a member of the Division of Medical Sciences of the National Research Council.

Among his articles published in our *Transactions*, I find "Modern Conception of the Pathology of Bright's Disease" (1934), "Tumors in Cold-Blooded Animals" (1940), and "Studies on Epidemic Hepatitis and Its Sequelae" (1948). I do not recall remarks by him from the floor at meetings of the College, but if made, they were sure to be constructive, brief and clear.

His publications, over a hundred in number, show how planned experiments occupied more and more of his time and interest. His volume of Collected Reprints in our Library contains 25 papers and 7 more appear in the card catalogue. We may hope that someday it will show a complete bibliography of his scientific work.

Dr. Lucké was first married (1917) to Dr. Marion Hague Rea, an able practitioner who, at the time of her death, in 1946, was visiting physician in two of our hospitals, and one of the earlier women to be elected a Fellow of this College. Their son, Balduin, and a granddaughter survive.

His devotion to professional interests left but little time for play. His recreations, which he heartily enjoyed, were few and simple: gardening, horseback riding, country walks to study birds and animal life, an occasional visit to the Tetons for some fishing and ranch life, and, as time permitted, reading novels and biographies. As his health began to fail, he was forced to cut down on some of his professional activities, and was shielded from strain in every possible way by his devoted wife, Helen Hughes Norris Lucké, to whom he had been married for several years. Even when he was occasionally confined to bed with a cardiac or pulmonary "episode", the write-up or study of data of some current work proceeded as usual. The various Washington meetings too frequently demanded his presence, but their problems were close to his heart, his opinions highly respected and he undoubtedly got much pleasure from the contacts they afforded. He died suddenly at his home from the results of severe long-standing coronary sclerosis with acute terminal occlusions and was buried in Arlington National Cemetery with full military honors.

The example and achievements of this accomplished Fellow of the College will last long in the memories of his friends and colleagues.

Memoir of John Francis McClosky (1877–1951)*

By JOSEPHUS TUCKER ULLOM

JOHN FRANCIS McCLOSKEY was born March 20, 1877, on the Erdenheim Stock Farm in Montgomery County near Chestnut Hill. He was the second son and third child born to John and Anna Lawless McCloskey. One sister, Sister Nicolita of the Sisters of St. Joseph, and one brother, Dr. Edward W. McCloskey, survive him. Three brothers, Anthony, Leo and James have died.

He was educated in the public schools of Montgomery County and later in the parochial schools of Philadelphia, graduating from the Catholic High School in 1897. He entered the University of Pennsylvania Medical School in the fall of 1897 and graduated in 1901.

In the spring of 1898, at the outbreak of the Spanish-American War, he enlisted in Battery "A" and served until the end of the war. His outfit did not see action but did get to Puerto Rico.

In the autumn of 1898 he returned to the Medical School and the study of medicine. During his student days he played center on the football team and made his letter in '98, '99 and 1900, winning All-American mention in 1900. He also played on the water polo team and was Captain of the championship team of 1900.

Following his graduation in 1901, he interned at St. Mary's Hospital in Philadelphia for one year and located in Chestnut Hill in the autumn of 1902. He soon gained a very large general practice in Chestnut Hill as he was well and favorably known in that locality. He was anxious, however, to be a surgeon and became associated in the fall of 1903 with Dr. Radcliffe Cheston and Dr. Russell Johnson, two prominent physicians of Chestnut Hill, and Dr. J. Murray Ellzey, a surgeon and practitioner, in the founding of the Chestnut Hill Hospital. Its first home was a pair of small houses on Gravers Lane, but by 1907 it had developed to such an extent that a new home was imperative and a large mansion at 8837 Germantown Avenue was purchased and converted to hospital use.

During these early years Dr. McCloskey worked hard at his practice and his surgery, visited many clinics in this country and in Europe, and became an accomplished surgeon.

He was visiting physician for many years to the Pennsylvania School for the Deaf and he was also visiting physician to the Chestnut Hill Academy.

In the summer of 1915 he went to France and worked at the American Ambulance from July to October, driving an ambulance part of the time. The next year he went over again and stayed some time, bringing back to this country the technic for the use of Dakin's Solution and Amberine, a treatment for burns.

In 1917 he enlisted in the United States Army and went to France in January 1918. He was surgeon in Evacuation Hospital № 2 and was with the Army during the campaign of the Argonne. Following the Armistice he was located with his outfit in Germany. He was mustered out in March 1919 with the rank of Lieutenant-Colonel.

After his return he resumed his work in Chestnut Hill. In 1932 he was appointed Clinical Professor of Surgery in the Woman's Medical College, a position he held until 1942 when he was retired on age. He was also on the staff of the Skin and Cancer Hospital for several years.

In 1933 Dr. McCloskey was instrumental in securing the Morris Arboretum for the University of Pennsylvania. Miss Lydia Morris

* Prepared, and published, at the request of the Council of the College of Physicians of Philadelphia. Read before the College, 1 April 1952.

was his patient and she and her brother, Mr. John T. Morris, had long been interested in horticulture and on their large and beautiful estate in Chestnut Hill they had a remarkable collection of trees, shrubs and flowers. Through Dr. McCloskey's efforts the estate was given to the University of Pennsylvania. He was a director of the Morris Arboretum until his death.

In 1936 he was elected Register of Wills and served for four years. He applied himself to his duties with his usual zest and made an excellent official. Mr. Boyle, his lieutenant, who had been in the office for many years, gave him high praise.

He was a founder and board member of the Chestnut Hill Title and Trust Company and served on the board after its merger with the Broad Street Trust Company. He was a member of the Fairmount Park Commission, being appointed in 1942.

Dr. McCloskey was a member of the Philadelphia Academy of Surgery, the American College of Surgeons, the College of Physicians of Philadelphia, the Philadelphia County Medical Society, the Pennsylvania State Medical Society and the American Medical Association.

He belonged to the Nu Sigma Nu Medical Fraternity, the Racquet Club, the Whitemarsh Valley Country Club, the Philadelphia Cricket Club, the Benjamin Franklin Pepper Post of the American Legion and the Henry C. Egbert Camp of United States Spanish War Veterans. He was a director of the Varsity Club of the University of Pennsylvania, also recipient of the Certificate of Merit of the Varsity Club.

Dr. McCloskey was united in marriage on October 15, 1917 with Miss Pauline Grotz of Philadelphia. Of this union four sons were born: John F. Jr., Robert E., Paul W. and Thomas. The three older boys survive their father. Thomas died in 1944.

Dr. McCloskey was a cheerful, optimistic, courageous individual. He was always willing to do anything to help a brother practitioner or a patient. Many a night have I seen him operate when I knew he had had a hard day. He was a skillful and conservative surgeon. His judgment was excellent, his patience inexhaustible. His results were uniformly good.

He possessed an extraordinarily fine disposition. He never criticized another person. In the many years of our association I cannot remember any occasion where he criticized a consultant, a brother practitioner or a patient. If he had a feeling that he had been badly treated, he kept it to himself. Dr. Osler states that a doctor should possess equanimity. This he had to a superlative degree. I never knew him to show any emotion no matter what the circumstances.

He was ever kind and considerate and ready to go to the defense of a weaker or less fortunate friend. One of his early schoolmates told me how he had thrashed a bully in the school who had attacked my informant, a smaller boy. On one occasion he found the coach of a small college football team beating one of the players because of the loss of a game. The action took place under the Franklin Field grandstand and McCloskey happened to pass by. He gave the older man a verbal and physical castigation that he remembered to the end of his days.

He was an excellent companion, an interesting raconteur and a faithful and loyal friend. He will be sadly missed in Chestnut Hill. He was beloved by all, both rich and poor. I think it is no exaggeration to say that he was the best known and most popular citizen of that community. For many years he was known as Dr. John, first to distinguish him from his brother, later as a term of affection.

On the evening of November 21st, 1951, the Philadelphia County Medical Society gave a dinner and presented plaques to those physicians who had practiced medicine for fifty years. There were seventeen men present and one woman. There were ten graduates of the University of Pennsylvania. McCloskey seemed in good spirits and it was an occasion enjoyed by all. The next morning I was shocked to receive a message from Dr. Edward McCloskey, asking me to come to see his brother who he said was in mortal pain. I found him dead on my arrival a few minutes later. He apparently died of a coronary occlusion.

Memoir of Francis Wharton Sinkler (1877–1954)*

By JOHN B. CARSON

FRANCIS WHARTON SINKLER was born on July 14, 1877 and died January 2, 1954.

He was the son of Dr. Wharton Sinkler, who had been a Vice-President of the College and a distinguished Philadelphia physician. His mother was Ella Brock.

He spent his whole life in Philadelphia, first attending the Blight School, he went from it to the Episcopal Academy where he graduated, to enter the University of Pennsylvania.

He graduated from the College department of the University of Pennsylvania in 1897 with the degree of A.B. and from the Medical Department in 1900.

After serving as Resident Physician in the Episcopal Hospital in Philadelphia, he commenced the practice of medicine under the aegis of his father, who was chiefly interested in neurology.

Then followed an active life as a practitioner and also as a manager and trustee of different charitable and philanthropic institutions.

As a practitioner he was well liked and trusted by his patients for his sound common sense, good judgment and sincerity.

He served as Attending Physician to the Episcopal Hospital and the Orthopedic Hospital and Infirmary for Nervous Diseases and was at one time Associate Professor of Neurology in the Graduate School of Medicine of the University of Pennsylvania.

He had also been a Trustee of the Episcopal Academy, Secretary and President of the Philadelphia Dispensary, President of the Pennsylvania Epileptic Hospital and Colony Farm, Chairman of the Aid Association of the Philadelphia County Medical Society and Examiner for the Society for Relief of Widows and Children of the Protestant Episcopal Church.

During the latter years of his life he was a manager of the Episcopal Hospital and a Vestryman of the Church of the Redeemer in Bryn Mawr, Pennsylvania.

Dr. Sinkler was elected a Fellow of the College of Physicians in 1907 and also was a member of the following Societies: Philadelphia County Medical Society, Pennsylvania State Medical Society, American Medical Association, American Neurological Society and the Philadelphia Pathological Society.

He was a member of the Phi Kappa Sigma Fraternity, the University Club and the University Barge Club.

On April 14, 1914, he married Mildred Scott Pearce and, besides his widow, four daughters survive him; Mrs. Herbert W. Goodall, Jr., Mrs. Millard H. Jackson, Jr., Mrs. Edward T. Stuart, Jr., and Mrs. H. Gordon Fraser, Jr.

Dr. Sinkler lived on Rose Lane in Bryn Mawr, Pa., and was interested indoors in carpentry and outdoors in the study of trees.

He died following a long illness which had curtailed his activities during the late years of his life.

* Prepared, and published, at the request of the Council of the College of Physicians of Philadelphia.

Transactions of the Sections

SECTION ON GENERAL MEDICINE

25 October 1954

HIRSUTISM: A MANIFESTATION OF JUVENILE HYPOTHYROIDISM. William H. Perloff, M.D. (Discusser: Norman G. Schneeberg, M.D.) (*Abstract 1, below*)

ARTHRITIS MUTILANS WITH CHONDROLYSIS AND THE SICCA SYNDROME: REPORT OF A CASE. Fred B. Rogers*, M.D., and John Lansbury, M.D. (Discusser: Ralph A. Jessar*, M.D.) (*Abstract 2, below*)

STRESS AND GASTRIC SECRETION: ITS POSSIBLE IMPORTANCE IN THE PSYCHOSOMATIC MECHANISM INVOLVED IN PEPTIC ULCER. Harry Shay, M.D., and David C. H. Sun*, M.D. (*Abstract 3, below*)

COMPARATIVE EFFECTS OF LOCAL AND SYSTEMIC ANTIBIOTIC THERAPY IN PREVENTION OF TRAUMATIC BACTEREMIA. R. S. Pressman, M.D., and I. B. Bender*, D.D.S. (Discusser: Ned B. Williams*, PH.D., D.D.S.) (*Abstract 4, below*)

22 November 1954

CHRONIC LEAD POISONING WITH MYXEDEMA: IMPROVEMENT ON VERSINATE THERAPY. Howard U. Kremer*, M.D. and Martin N. Frank*, M.D. (Discusser: John Reinhold*, PH.D.) (*Abstract 5, below*)

METABOLISM OF RADIOIODINATED HUMAN GAMMA GLOBULIN IN PATIENTS WITH HEPATIC CIRRHOSIS AND ASCITES. W. Paul Havens, Jr., M.D., James Dickensheets*, M.D., James N. Bierly*, PH.D., and Theodore P. Eberhard, M.D. (Discusser: Henry J. Tumen, M.D.) (*Abstract 6, below*)

SPONTANEOUS RUPTURE OF THE ESOPHAGUS: CLINICAL AND EXPERIMENTAL STUDY. Tibor Bodi*, M.D., and C. Wilmer Wirts, M.D. (Discusser: John Y. Templeton, 3d,* M.D.) (*Abstract 7, below*)

THE CHRONIC LEG ULCER. Meyer Naide, M.D. (Discusser: Jonathan E. Rhoads, M.D.) (*Abstract 8, below*)

* *By invitation.*

SECTION ON MEDICAL HISTORY

18 October–22 November 1954

SEVENTH SERIES OF WEEKLY LECTURES FOR MEDICAL STUDENTS[1]. Richard H. Shryock*, PH.D., and Owsei Temkin*, M.D.

5 November 1954[2]

S. WEIR MITCHELL, THE NEUROLOGIST[3]. I. S. Wechsler*, M.D.

S. WEIR MITCHELL, AS MAN OF LETTERS[3]. Ernest Earnest*, PH.D.

SECTION ON OPHTHALMOLOGY[4]

27 September 1954

(Special Meeting)

OPHTHALMIC AND OTHER MEDICAL PROBLEMS DEALING WITH THE ABORIGINES IN THE UNDERDEVELOPED AREAS OF N. W. AUSTRALIA. Ida Mann*, D. SC.

21 October 1954

HYALURONIC ACID AND HYALURONIDASE IN AQUEOUS HUMOR AND THE ANTERIOR CHAMBER ANGLE. Ernst Bárány*.

18 November 1954

RESULTS OF OPERATIONS FOR GLAUCOMA, WITH SPECIAL REFERENCE TO CYCLOELECTROLYSIS AND IRIDOCORNEOSCLEROTOMY. Conrad Berens*, M.D. (*Seventeenth Annual de Schweinitz Lecture*)

[1] For the subjects and assignment of speakers, see the program of the 6th series, *Trans. & Stud.*, April, 1954, p. 162.

[2] Joint meeting with the Philadelphia Neurological Society.

[3] Published in the *Trans. & Stud.*, February, 1955.

[4] Abstracts of the presentations at this Section customarily appear in the *American Journal of Ophthalmology* and the *A. M. A. Archives of Ophthalmology.*

16 December 1954

Leiomyoma of the Iris: Case Report and Review of the Literature. Wayne L. Erdbrink*, Lt., MC, USN. (Discusser: John S. McGavic, M.D.)

Congenital Bilateral Abducens—Facial Paralysis—Moebius Syndrome. Jules M. Yasuna*, M.D., and Nathan S. Schlezinger, M.D.

Blepharophimosis—the Surgical Correction. Edmund B. Spaeth, M.D.

SECTION ON OTOLARYNGOLOGY[5]

17 November 1954

(A Review of Hearing Testing)

Clinical Evaluation of the Older Methods. Robert J. Hunter, M.D.

Pure Tone and Speech Audiometry. Frederick Harbert*, M.D.

Hearing Testing in Young Children. David Myers, M.D., and Milton Brutten*, PH.D. (Discusser: Douglas Macfarlan, M.D.)

15 December 1954

Acute Cerebellar Abscess of Otic Region: Report of Two Cases. Louis E. Silcox, M.D., and Thomas Flynn*, M.D.

Nasopharyngeal Fibroma. Romeo A. Luongo, M.D.

Post-operative Nasopharyngeal Fibrosis. George L. Whelan, M.D.

An Unusual Bronchoscopic Case. William A. Lell, M.D.

Reticulum Cell Sarcoma of the Paranasal Sinuses. Benjamin H. Shuster, M.D., and Allan R. Shuster*, M.D.

Abstracts

Abstract 1

Hirsutism: a Manifestation of Juvenile Hypothyroidism. William H. Perloff, M.D.

An unusual but typical type of hirsutism involving the back, shoulders, outer aspects of the arms and legs and to a lesser degree the sides of the face has been observed in four hypothyroid children. The administration of desiccated thyroid relieved this distressing symptom within six to eight months. It is therefore thought that this type of hirsutism is a manifestation of juvenile hypothyroidism.

Abstract 2

Arthritis Mutilans with Chondrolysis and the Sicca Syndrome: Report of a Case. Fred B. Rogers, M.D., and John Lansbury, M.D.

A case of arthritis mutilans of six years' duration is described in a 61 year old white woman. This report is believed to be the twenty-eighth case of arthritis mutilans published in medical literature since the first description by Pierre Marie and A. Léri in 1913. Cardinal features in this case were diffuse skeletal osteoporosis, spotty, severe joint destruction with surprising preservation of function, and grotesque deformities of the hands and feet (main, doigt et pied en lorgnette). Bizarre dissolution of external nasal, aural and laryngeal cartilages and coexistence of the sicca syndrome (Gougerot-Sjögren Disease) were of added importance in this case. Widespread, severe destruction of skeletal cartilage had apparently followed injections of chorionic gonadotropins derived from human pregnancy urine.

Arthritis mutilans has been generally considered a rare variant or extreme manifestation of rheumatoid arthritis. Although described in the past under a variety of names, this disease appears to be of somewhat more frequent incidence and less recent origin than usually assumed. The literature on arthritis mutilans is reviewed, differential diagnosis and possible endocrine relationships discussed, and a case added to previous reports.

The association of this rare form of arthritis with marked chondrolysis and the sicca syndrome adds emphasis to the concept that rheumatoid arthritis is not a single disease but

[5] Abstracts of the presentations at this Section customarily appear in the *A. M. A. Archives of Otolaryngology.*

rather a general reaction pattern of multiform character. This broadened viewpoint regards its joint manifestations as localized processes superimposed upon a widespread tissue disorder throughout the body.

Abstract 3

STRESS AND GASTRIC SECRETION: ITS POSSIBLE IMPORTANCE IN THE PSYCHOSOMATIC MECHANISM INVOLVED IN PEPTIC ULCER. Harry Shay, M.D., and David C. H. Sun, M.D.

Gray has shown in man that ACTH, cortisone, emotional as well as physical stress will stimulate gastric secretion. This will occur when both vagi have been cut and after subtotal gastrectomy. Recently Porter, French and their associates, in monkeys, have demonstrated that stimulation of the anterior hypothalamic area will produce an early gastric secretory response with its peak between 1 and 2 hours. This response can be prevented by previous bilateral vagotomy. Stimulation of the posterior hypothalamic area will also produce a gastric secretory response but the peak will come later at approximately 3 hours. This response can be prevented by previous adrenalectomy. With insulin hypoglycemia these workers were able to show a composite curve which they were able to resolve into the early and late components. We have demonstrated that in man, too, insulin hypoglycemia will stimulate a double curve of gastric secretion and we have been able to relate the early curve to the intact vagi and the late curve to the presence of at least one intact adrenal gland.

Abstract 4

COMPARATIVE EFFECTS OF LOCAL AND SYSTEMIC ANTIBIOTIC THERAPY IN PREVENTION OF TRAUMATIC BACTEREMIA. R. S. Pressman, M.D., and I. B. Bender, D.D.S.

Most previous attempts to prevent traumatic bacteremia (post-extraction) have involved the preoperative administration of antibiotics by the parenteral route as a means of attacking the organisms after they have entered the blood stream. The following study tests the hypothesis that bacteremias can be prevented by attacking the bacteria at their source, the gingival sulcus, before they enter the blood stream.

A comparative study of effectiveness of intramuscular penicillin and two different types of oral antibiotic troches, one with penicillin and one without, was made on the bacterial population of the mouth and on the bacteremia following extraction of two or more teeth.

The results showed that the bacterial population of the mouth was markedly reduced in the troche studies while in the intramuscular penicillin group there was no reduction. After the troche containing penicillin was dissolved in the mouth for one-half hour, the effect on the bacteremias was equally as good and under certain conditions better than parenteral penicillin.

It was demonstrated that in cases of heavy trauma of extraction, parenteral penicillin was ineffective, while the troches containing penicillin displayed a therapeutic effect of a statistically significant degree.

The troches are suggested as an adjunct of, not as a substitute for, parenteral administration of antibiotics. The troche that does not contain penicillin may be used in patients known to be penicillin sensitive.

Abstract 5

CHRONIC LEAD POISONING WITH MYXEDEMA: IMPROVEMENT ON VERSINATE THERAPY. Howard U. Kremer, M.D., and Martin N. Frank, M.D.

This case is of interest because of the coexistence of chronic lead poisoning and myxedema exhibited in a man some thirty-five years after exposure to lead. The evidence of lead intoxication was a low grade hemolytic anemia, basophilic stippling, increased blood lead level on several occasions and increased urinary excretion of lead after the deleading effect of Versinate. In addition there were signs of a peripheral neuropathy.

It is noteworthy that this case was diagnosed for some time as pernicious anemia and received several trials of liver extract and Vitamin B_{12} therapy without noticeable benefit hematologically. Furthermore the anemia did not respond until large doses of Vitamin C were added.

The myxedematous state responded dra-

matically to adequate thyroid replacement therapy. However, because of chronic coronary insufficiency the full dosage regime of thyroid substance could not be given.

This case gave us opportunity to try a new type of therapy in chronic lead poisoning, namely the use of a chelating agent as Calcium Versinate. After two doses of the agent, the urinary excretion of lead increased remarkably. This was added proof of the premise that this man had lead stored in his tissues like bone.

Abstract 6

METABOLISM OF RADIOIODINATED HUMAN GAMMA GLOBULIN IN PATIENTS WITH HEPATIC CIRRHOSIS AND ASCITES. W. Paul Havens, Jr., M.D., James Dickensheets, M.D., James N. Bierly, PH.D., and Theodore P. Eberhard; M.D.

The fate of intravenously injected normal human gamma globulin labeled with I^{131} was studied in five adult patients with hepatic cirrhosis and in two adult controls. In four cirrhotics who had ascites, detectable radioactivity was present in the ascitic fluid 1–2 hours after the intravenous injection of 100 μc iodinated gamma globulin. It rose sharply thereafter, and at the end of 24 hours large amounts were found. Following this, the radioactivity increased slightly during the next 3–5 days, and then declined in parallel with the decline of radioactivity in the serum. The amounts of radioactivity in the ascitic fluid and serum were not greatly dissimilar after equilibration was reached (after 4–6 days), but the concentration in the ascitic fluid was always less than that found in the serum during the period of observation.

The decline of radioactivity in the blood was rapid in all seven subjects during the first few days and could usually be resolved into at least three components of diminishing steepness of slope before equilibration was reached. In the patients with ascites, this rapid disappearance of the faster components was partially accounted for by the transfer of large amounts of radioactivity to the ascitic fluid. In two such patients, the urinary excretion of radioactivity measured only 4.24% and 7.82%, respectively, during the first 24 hours after injection. In contrast, 14.5%–32.0% of the injected dose was eliminated during the first 24 hours in the urine of two controls and one cirrhotic without ascites. Likewise, during the first five days, approximately 45%–67% of the injected dose was excreted in the urine by the latter patients, while two patients with ascites excreted only 10% and 28%, respectively. Both of these lost considerable amounts of ascitic fluid by drainage through paracentesis during this period.

These results are in accord with those of others†, indicating that the exchange of gamma globulin between the blood and ascitic fluid of patients with hepatic cirrhosis occurs at a constant rate after equilibration is reached and if stable conditions are maintained. The half-life of the injected gamma globulin may be calculated from data obtained by measuring the amounts of radioactivity in the blood, ascitic fluid or the urine over a period of 2–3 weeks after equilibration.

Abstract 7

SPONTANEOUS RUPTURE OF THE ESOPHAGUS: CLINICAL AND EXPERIMENTAL STUDY. Tibor Bodi, M.D., and C. Wilmer Wirts, M.D.

The clinical course of five patients will be described; two survived following surgery and three came to necropsy. In addition the results of our experimental study of the mechanism whereby this phenomenon is produced will be presented. We have attempted to reproduce the process, as it occurs spontaneously, more closely than was done in previous experiments by others. Hydrostatic pressure was applied intraluminally to the esophagi of cadavers. Retrograde injection of contract material under pressure and fluoroscopic control made it possible to observe the sequence of events in the esophagus left intact in situ. The typical protrusion was noted on the lower left lateral third of the organ and the ruptured specimens were similar to those seen clinically.

† Bauer, F. K., Blahd, W. H., Fields, M., and Getchell, G.: Ascitic fluid and plasma protein exchange in cirrhosis of the liver. Studies with radioiodinated human serum albumin and gamma globulin, Metabolism **3:** 289–296, (July) 1954.

Spontaneous rupture of the esophagus occurs more often than is suspected. Its symptomatology involves the differential diagnosis of thoracic and abdominal emergencies. There is usually a history of vomiting, retching, persistent chest and/or abdominal pain and hematemesis. The most common physical signs are those of shock, cyanosis, rapid shallow respirations, left side hydropneumothorax, mediastinal and subcutaneous emphysema, abdominal rigidity and tenderness. It is remarkable that none of the three patients autopsied had subcutaneous emphysema; two of them had chronic duodenal ulcers; all three revealed a typical rent on the left lateral lower third.

Early detection is essential and is possible in most instances clinically if the syndrome is thought of, but thoracentesis and lipidol swallow serve to establish the diagnosis. The treatment is thoracotomy and suture of the defect; thoracotomy and drainage are less effective.

Abstract 8

THE CHRONIC LEG ULCER. Meyer Naide, M.D. Chronic leg ulcers are difficult and discouraging conditions to treat. Despite the fact that many patients with these ulcers undergo long periods of pain and disability, this condition remains relatively neglected falling somewhere between the surgeon, the dermatologist and the internist or general practitioner. In some countries it has been found that more working days have been lost through chronic leg ulcers than through tuberculosis. There are approximately 1,000,000 patients with chronic leg ulcers in this country.

These ulcers are ordinarily called varicose ulcers, stasis ulcers, post-phlebitic or gravitational ulcers. Although varicose veins are frequently present in these patients, they are responsible for the ulcers in only a small percentage of the cases. In most patients deep thrombophlebitis or local phlebitis is the cause of the chronic leg ulcer. This deep vein thrombosis or incompetence results in back pressure and dilatation of the veins with increased capillary pressure and edema. Eventually there is induration of the skin. Then trauma opens the skin, infection occurs and a chronic leg ulcer appears. Sensitization to fungi and to medication are common additional factors.

There are numerous other causes for leg ulcers, including ischemia, blood dyscrasias, trophic ulcers in diabetes and following poliomyelitis, ulcers due to pernio, the ischemic hypertensive ulcer, ulcers due to erythema nodosum, lymphedema, trauma, malignancy and, finally, due to malingering. The post-phlebitic ulcer, however, represents 70 to 85% of chronic leg ulcers.

Innumerable methods of treatment have been proposed for chronic leg ulcers. Anything that could be applied locally has been used by these patients. Most leg ulcers can be healed by placing the patient in bed with the leg elevated. However, most patients have to be treated on an ambulatory basis and this can be done with present day methods in a large number of cases. Compression types of bandages are available today which are superior to the old Unna paste bandage or gelatin boot type of treatment. A medicated wet bandage is applied to the skin and on top of this an elastic adhesive bandage is applied for firm compression. This tends to prevent edema and in addition permits the contraction of the muscles against resistance and thus makes for more efficient outflow of blood from the leg. If the bandage is not tolerated, cleaning up the ulcer with physiologic saline for several days and using neomycin ointment is of value. Applying some of the patient's blood directly to the ulcer may heal some ulcers if the surface is not necrotic. Blocking the sympathetic ganglia with Etamon or Dibenzyline may be of value for relief of pain.

Ischemic ulcers may require lumbar sympathectomy.

Various surgical procedures are of value such as skin grafting and, in some patients, vein ligation.

Once the ulcer is healed these patients must wear an elastic stocking or support for the rest of their lives. Control of dermatophytosis is important to reduce sensitization to fungi.

List of College Lectures, 1954

6 January 1954

Richards, Dickinson W. Physiological Behavior and Therapeutic Use of Plasma Volume Expanders. (Mary Scott Newbold Lecture LXVIII; *Transactions & Studies*, June, 1954)

3 February 1954

Page, Irvine H. The Treatment of Arterial Hypertension. (Nathan Lewis Hatfield Lecture XXXVIII; *Transactions & Studies*, August, 1954)

3 March 1954

Rusk, Howard A. The Physician and the Changing World. (James M. Anders Lecture XXXI)

7 April 1954

Katz, Louis N. The Mechanism of Cardiac Failure. (Mary Scott Newbold Lecture LXIX; *Transactions & Studies*, August, 1954)

*12 May 1954**

Gibbon, John H., Jr. Cancer of the Lung.

6 October 1954

Stetten, DeWitt, Jr. Biochemical Explorations of Certain Disturbances of Carbohydrate Metabolism. (Alvarenga Prize Lecture XIV; *Transactions & Studies*, February, 1955)

*3 November 1954**

Gordon, John E. Population Pathology. (James M. Anders Lecture XXXII; scheduled for publication in the June, 1955, issue of the *Transactions & Studies*)

1 December 1954

Cohen, Seymour S. The Chemical Pathology of the Virus-Infected Cell. (Thomas Dent Mütter Lecture LXVII; *Transactions & Studies*, February, 1955)

* Joint Meeting with the Philadelphia County Medical Society.

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Dolores Magasich

Editorial

THE *Transactions of the College of Physicians of Philadelphia* is, so far as American medical society publications go, a rather old party. The first volume—hopefully, if fruitlessly, designated "Volume 1. Part 1."—was published in 1793. But forty-eight years were to elapse, as it happened, before the transactions of the College came to be published on a reasonably continuous basis. The present issue concludes the 84th volume to see the light of day since publication was belatedly resumed in 1841. Few American medical societies could lay themselves down on the analyst's couch with a comfortable sense of having matched the College in the discharge of this obligation to its Fellows—and, ultimately, to history.

Interestingly enough, when the phoenix rose from its ashes, in 1841, it was in the form of a quarterly publication, which was carried on (with some unquarterly hiatuses) through 1874. There then began, in 1875, a so-called third series, impressive annual (briefly, biennial) bound volumes—55 of them—that carried our story through 1932. By that time, it had become clear that so leisurely a manner of publication ill served those interested in obtaining prompt access to the College's scientific transactions. And the bound volumes were expensive. Accordingly, a fourth series was begun, in 1933, the volumes comprising, originally, semi-annual, unbound issues, with occasional supplements. Four volumes were published in this form; a fifth (for 1937) was published in a single number.

This arrangement, too, did not seem to be altogether satisfactory. Simultaneously, there had developed considerable feeling that the *Transactions* might advantageously be used also to draw wider attention to the historical resources of the College's great library. With 4th series, vol. 6, no. 1, June, 1938, there was begun what was in effect a 5th series of the *Transactions*—though, mercifully, it was not so designated. The annual volume, reverting to the enlightened plan of the mid-19th century, again comprised four numbers, to permit prompt publication of immediately useful material. The words "& Studies" were added to the title, to signalize the inclusion of historical studies emanating from the library and the meetings of the College's Section on Medical History. The printing was placed in the hands of the Waverly Press; the editorship, in the hands of the then Librarian of the College, who had edited the preceding volume.

That editor, having now completed seventeen volumes of this "5th series", and having new College duties of absorbing interest, is, at his request, graciously being relieved of further responsibility in the publication of the *Transactions & Studies*. As he takes leave of this rewarding—if, under the circumstances, also exacting—task, he feels himself under no compulsion either to seek to excuse his editorial failings or to imagine compensatory virtues. He simply did the best he could, as every conscientious workman does, and that is that. On the other hand, this editorial could not properly close without giving expression to a warm sense of appreciation of the heartening support invariably forthcoming over the years from a long line of Publication Committees, and from colleagues at the Waverly Press—notably, in latter years, from their Mr. William A. Sager. Still less could it close without introduction of the new editor, Mr. William K. Beatty, of the library staff, who, one may rest assured, will see the old party through to a better life than she has ever lived before.

And so, appropriating the possibly ambivalent words the old scribes used to record the end of one of their labors, *Laus deo.*

W. B. McD., 2d

Fellows

December 31, 1954

ELECTED

1952. Abelson, Neva Martin, 32 Woodale Rd.
1948. Adelizzi, Richard A., 1723 S. Broad St.
1926. Adler, Francis Heed, 313 S. 17th St.
1949. Aegerter, Ernest E., 3400 N. Broad St.
1953. Agerty, Horst A., 1111 N. 63rd St. (31)
1914. Aiken, Thomas G., Berwyn, Pa.
1936. Alexander, Fay Knight, Germantown Professional Bldg., Greene and Coulter Sts.
1947. Allbritten, Frank F., Jr., Univ. of Kansas Med. Center, Kansas City 3, Kansas.
1932. Allen, Frederick H., 1711 Fitzwater St.
1953. Allman, David B., 104 St. Charles Pl., Atlantic City, N. J.
1935. Alpers, Bernard J., 111 North 49th St.
1930. Appel, Kenneth E., 111 N. 49th St.
1905. Appelman, Leighton Francis, 308 S. 16th St.
1935. Armitage, George L., 400 E. 13th St., Chester, Pa.
1922. Arnett, John H., 2116 Pine St.
1942. Aronson, Joseph D., Henry Phipps Institute, 7th and Lombard Sts.
1952. Ash, Rachel, 5636 Pine St. (43)
1952. Aston, Melville J., 2507 S. 21st St.
1944. Atkins, Joseph P., 1201 Knox Rd., Wynnewood, Pa.
1935. Atlee, John L., Jr., 37 E. Orange St., Lancaster, Pa.
1952. Atlee, William A., 37 E. Orange St., Lancaster, Pa.
1954. Austin, George M., 3400 Spruce St. (4)
1935. Bach, Theodore F., 1900 Rittenhouse Sq.
1942. Bachman, Carl, Univ. of Pa. Hospital.
1937. Bacon, Emily P., 1930 Chestnut St.
1952. Baier, Howard N., 3401 N. Broad St.
1952. Baker, Howard W., 3401 N. Broad St.
1946. Baker, Walter W., 255 S. 17th St.
1940. Barba, Philip S., 5919 Greene St.
1943. Barden, Robert P., 8835 Germantown Ave.
1911. Barnard, Everett P., 1820 Rittenhouse Sq.
1939. Barnshaw, Harold D., 406 Cooper St., Camden, N. J.
1939. Bartle, Harvey, Jr., 133 S. 36th St.
1931. Bates, William, 2029 Pine St.
1932. Batson, Oscar V., 3502 Hamilton St.
1921. Bauer, Edward L., 5501 Greene St. (44)
1933. Bauer, John T., 312 E. Second St., Moorestown, N. J.
1939. Baumann, Frieda, 1914 Panama St.
1908. Beardsley, E. J. G., 1919 Spruce St.
1930. Beardwood, Joseph T., Jr., 2031 Locust St.
1952. Bedrossian, E. Howard, 2027 Spruce St.
1949. Beecham, Clayton T., Greene & Coulter Sts.
1935. Beerman, Herman, 2422 Pine St.
1942. Behrend, Albert, 255 S. 17th St.
1945. Behrend, Bernard, 5910 Greene St.
1934. Behrend, Moses, 255 S. 17th St.

1949. Beizer, Lawrence H., 255 S. 17th St.
1930. Belk, William Parks, 433 Owen Rd., Wynnewood, Pa.
1936. Bell, Benjamin Tertius, Abington Medical Bldg., Keith & York Rds., Abington, Pa.
1947. Bellet, Samuel, 2021 Spruce St.
1954. Bello, Carmen T., 3401 N. Broad St. (40)
1952. Bennett, George A., 1025 Walnut St.
1943. Berk, J. Edward, 6767 W. Outer Drive, Detroit 35, Mich.
1941. Bernstein, Mitchell, 7609 Mountain Ave. (17)
1951. Bernstine, J. Bernard, 255 S. 17th St.
1937. Bertolet, J. Allen, 4024 Timber Lane.
1918. Billings, Arthur E., 2020 Spruce St.
1952. Bird, Gustavus C., Jr., 3401 N. Broad St.
1949. Bishop, Edward H., 255 S. 17th St.
1933. Bishop, Paul A., Pennsylvania Hospital.
1944. Blady, John V., 340 Fishers Rd., Bryn Mawr, Pa.
1952. Blake, Paul O., 273 N. Lansdowne Ave., Lansdowne, Pa.
1951. Blank, Harvey, Squibb Institute, Georges Rd., New Brunswick, N. J.
1917. Block, Frank B., 305 Tabor Medical Bldg., York & Tabor Rds.
1949. Blumstein, George I., 2039 Delancey St.
1929. Bockus, Henry L., 250 S. 18th St.
1928. Boles, Russell S., Rittenhouse Plaza, 1901 Walnut St.
1923. Bond, Earl D., 111 N. 49th St.
1911. Bonney, Charles W., 255 S. 17th St.
1948. Bookhammer, Robert S., 209 Rittenhouse Claridge. (3)
1931. Bortz, Edward Le Roy, 2021 W. Girard Ave.
1921. Borzell, Francis Frank, 4940 Penn St.
1936. Bostwick, Delazon Swift, 106 Linwood Ave., Ardmore, Pa.
1928. Bothe, Albert E., 255 S. 17th St.
1928. Bothe, Frederick A., 255 S. 17th St.
1951. Boucot, Katharine R., 229 W. Upsal St.
1947. Bourland, Henry S., 2219 Garret Rd., Drexel Hill, Pa.
1923. Bower, John O., 2008 Walnut St.
1954. Bowers, Paul A., 2035 Locust St. (3)
1942. Bowie, Morris A., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1907. Bradley, William Nathaniel, 1725 Pine St.
1954. Bralow, S. Philip, 2104 Delancey Pl. (3)
1942. Branen, William, Whitby & Cypress Ave., Yeadon, Pa.
1921. Bransfield, John W., 2101 Spruce St.
1948. Braun, William, 406 Cooper St., Camden, N. J.
1953. Brav, Solomon S., 5575 N. Park Ave. (41)
1953. Breckenridge, Robert L., Jefferson Hospital. (7)
1951. Brinton, S. Jervis, Fishers Road, Bryn Mawr, Pa.
1946. Briscoe, Clarence Conway, 811 Spruce St. (7)
1953. Brobeck, John R., Univ. of Pa. School of Medicine. (4)
1952. Brody, Morris W., 1930 Chestnut St.
1948. Brogan, Edmund J., Thomas Wynne Apartment, Wynnewood, Pa.
1917. Bromer, Ralph S., 318 Milbank Road, Bryn Mawr, Pa.
1953. Brooke, John A., 1431 Spruce St. (2)
1936. Brown, Charles L., 1030 Indian Creek Rd.
1936. Brown, Clark E., Lankenau Hospital.
1932. Brown, Claude P., 1930 Chestnut St.
1919. Brown, Henry P., Jr., Willow Grove & Cherokee Avenues.

1939. Brust, Raymond W., 4710 Chester Ave.
1953. Bucher, Robert M., 3401 N. Broad St. (40)
1952. Bumgardner, Heath D., 3701 N. Broad St.
1953. Burbidge, J. Raymond, 163 Nassau St., Princeton, N. J.
1940. Burnett, W. Emory, 3401 N. Broad St.
1954. Burros, Harry M., 255 S. 17th St. (3)
1941. Butler, Miriam, Watersmeet, Glen Mills, Pa.
1907. Cadwalader, Williams B., 133 S. 36th St.
1928. Campbell, Edward H., 133 S. 36th St.
1952. Campbell, Edward W., 1318 Medical Arts Bldg.
1944. Campion, Richard J., Penllyn Rd., Springhouse, Ambler, Pa.
1931. Cantarow, Abraham, 1025 Walnut St.
1952. Cardone, John B., 343 N. 63rd St.
1935. Carey, Lawrence S., 330 S. 9th St.
1931. Cariss, Walter L., 4310 Walnut St.
1930. Carpenter, Chapin, 1930 Chestnut St.
1926. Carpenter, Howard Childs, 1805 Spruce St.
1917. Carson, John B., Newtown Square, Pa.
1937. Castallo, Mario A., 1621 Spruce St.
1943. Castigliano, S. Gordon, 853 Mt. Pleasant Rd., Bryn Mawr, Pa.
1949. Caswell, H. Taylor, 3401 N. Broad St.
1954. Catenacci, Alfred J., 1417 S. Broad St. (47)
1954. Cathcart, Richard T., 739 S. Broad St. (47)
1950. Chamberlain, Richard H., 3400 Spruce St.
1933. Chamberlain, W. Edward, Temple University Hospital.
1939. Chamberlin, George W., Reading Hospital, Reading, Pa.
1900. Chance, Burton, 317 S. 15th St.
1945. Chance, Burton, Jr., 1726 Spruce St.
1948. Chapman, John P., 71st St. & City Line Ave., Overbrook, Pa.
1950. Chapple, Charles C., Flourtown, Pa.
1954. Charny, Charles W., 2039 Delancey Pl. (3)
1939. Charr, Robert Kyun Kyun, 2038 Locust St.
1947. Chouké, Kehar S., P.O. Box 547, Kecoughton, Va.
1945. Cianfrani, Theodore, 1930 Chestnut St.
1939. Ciccone, Emmet F., 2021 Murray St.
1951. Clagett, Augustus H., Jr., 11400 Nemours Bldg., Wilmington, Del.
1929. Clark, Eliot R., 315 S. 41st St.
1934. Clark, Jefferson Hamer, 101 Maple Ave., Wyncote, Pa.
1951. Clark, John K., University Hospital, 36th & Spruce Sts.
1947. Clark, Thomas Williams, 400 E. Willow Grove Ave.
1947. Classen, Charles H., Cushman Rd. and Lancaster Ave., Rosemont, Pa.
1910. Cloud, J. Howard, 111 St. Pauls Road, Ardmore, Pa.
1903. Coates, George Morrison, 1721 Pine St.
1941. Cohen, J. Gershon, 255 S. 17th St.
1951. Cohen, Leon Solis-, 1422 Chestnut St.
1949. Cohen, Louis B., 1320 Arrott St.
1907. Cohen, Myer Solis-, 2110 Spruce St.
1953. Cohen, Robert V., 255 S. 17th St. (3)
1934. Colgan, Robert C., 5882 N. Marshall St.
1934. Collins, Leon Howard, Jr., 133 S. 36th St.
1943. Colonna, Paul C., Univ. of Pa. Hospital.
1949. Conger, Kyril B., 3401 N. Broad St.

1945. Coonel, Pauline, 47 E. Mt. Pleasant Ave.
1930. Cooper, David A., 1520 Spruce St.
1953. Cooper, Donald R., 133 S. 36th St. (4)
1947. Coppolino, John F., 1807 S. Broad St.
1952. Corbit, John D., Jr., 3717 Chestnut St.
1941. Cornelius, Chalmers E., 119 Summit Ave., Jenkintown, Pa.
1911. Cornell, Walter S., Board of Public Education, Parkway and 21st St.
1945. Corrigan, Patrick H., 1720 S. Broad St., Trenton, N. J.
1914. Corson, Edward F., 136 S. 16th St.
1946. Costello, Thomas J., 131 Pennsylvania Avenue, Bryn Mawr, Pa.
1924. Cowan, Alfred, 1930 Chestnut St.
1940. Cowan, Thomas H., 1930 Chestnut St.
1904. Craig, Frank A., 429 Montgomery Ave., Haverford, Pa.
1907. Crampton, George S., 2031 Locust St.
1947. Crane, A. Reynolds, 807 Spruce St.
1937. Crane, Martin P., 2412 N. Broad St.
1920. Creighton, William J., 37 S. 20th St.
1952. Crellin, J. Antrim, 1930 Chestnut St.
1941. Creskoff, Adolph J., 3400 Spruce St.
1917. Cross, Sumner H., P.O. Box 126, Jenkintown, Pa.
1921. Crossan, Edward T., R. D. #1, Conshohocken, Pa.
1904. Cruice, John M., 407 S. 22nd St.
1937. Crump, Jean, 1930 Chestnut St.
1937. Curtis, Lawrence, 255 S. 17th St.
1934. Custer, R. Philip, 126 Grays La., Haverford, Pa.
1938. Dannenberg, Arthur M., 235 S. 15th St.
1951. Daugherty, Earl A., 2025 W. Girard Ave.
1953. Davie, John H., 269 S. 19th St. (3)
1947. Davis, C. Nelson, 133 South 36th St.
1936. Davis, David M., 255 S. 17th St.
1951. Davis, J. Wallace, 135 S. 18th St.
1937. Davis, Perk Lee, P.O. Box 701, Paoli, Pa.
1935. Deaver, J. Montgomery, 1830 Delancey Pl.
1947. Dehne, Theodore L., Adams Avenue and Roosevelt Blvd.
1902. Dehoney, Howard, 240 S. 13th St.
1935. Deibert, Irvin Elmer, 538 Cooper St., Camden, N. J.
1948. Deichler, John W., 1930 Chestnut St.
1954. Deitrick, John E., 1025 Walnut St. (7)
1923. De Long, Perce, 37 S. 20th St.
1952. DeLuca, Charles Q., 255 S. 17th St.
1952. De Orsay, Ralph H., 1241 Lindale Ave., Drexel Hill, Pa.
1951. De Palma, Anthony F., 248 S. 21st St.
1928. Dewees, A. Lovett, Glen Mills, Del. Co., Pa.
1952. Digilio, Victor A., 2200 St. James Place.
1924. Dillon, Edward S., 2028 Delancey Pl.
1953. Dixon, James P., Dept. of Public Health, City Hall Annex. (7)
1920. Doane, Joseph C., 617 W. Hortter St.
1948. Dohan, Francis Curtis, 80 Princeton Road, Cynwyd, Pa.
1954. Donaldson, James B., 235 N. Broad St. (2)
1946. Donnelly, Andrew J., 33rd and Powelton Ave.
1942. Donnelly, Edward J., 1321 Spruce St.
1933. Donnelly, Joseph C., 6832 Ogontz Ave.

1937. Donnelly, Robert T. M., 255 S. 17th St.
1954. Downing, Daniel F., 554 Fairway Ter. (28)
1952. Drayer, Calvin S., 111 N. 49th St.
1949. Dripps, Robert D., 3400 Spruce St.
1935. Duane, William, Jr., Rittenhouse Club, 18th & Walnut Sts.
1944. Dublin, George J., 1930 Chestnut St.
1944. Dugger, John H., 3902 Vaux St.
1935. Duncan, Garfield G., 330 S. 9th St.
1937. Dunn, Charles W., 265 S. 19th St.
1951. Dunne, Francis S., 133 S. 36th St.
1953. Dupler, Donald A., 4028 Walnut St. (4)
1942. Durant, Thomas M., 3401 N. Broad St.
1947. Durkin, John Keenan, 34 W. Montgomery Ave., Ardmore, Pa.
1942. Dyer, W. Wallace, Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1935. Eads, John T., 2029 Delancey St.
1936. Easby, Mary Hoskins, Woman's Hospital.
1948. Eaton, Francis H., 4007 Chestnut St.
1953. Eberhard, Theodore P., Jefferson Hospital. (7)
1937. Edeiken, Joseph, 2130 Delancey Pl.
1944. Eger, Sherman A., 2029 Delancey St.
1949. Egoville, John W., 720 N. 63rd St.
1944. Ehrich, William E., 540 W. Hortter St.
1953. Eisenberg, Isadore J., 2117 Spruce St. (3)
1946. Elfman, Louis Kenneth, 6330 Lebanon Avenue.
1949. Elkinton, J. Russell, Oak Lane, Moylan, Pa.
1939. Ellis, Van Mashburn, 1530 Locust St.
1928. Ellison, Richard T., 8601 Stenton Ave.
1936. Ellson, J. Vernon, 807 Spruce St.
1904. Elmer, Walter G., 1801 Pine St.
1937. Elsom, Kendall A., 133 S. 36th St.
1934. Ely, William C., 3912 Chestnut St.
1932. Engel, Gilson C., 225 S. 17th St.
1945. English, O. Spurgeon, 3401 N. Broad St.
1942. Erb, William H., 133 S. 36th St.
1953. Erf, Lowell A., Jefferson Hospital. (7)
1950. Ersner, Matthew S., 1915 Spruce St.
1954. Evans, Harry D., Jr., 250 S. 18th St. (3)
1954. Evans, William W., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1948. Everts, Glenn S., 5515 Wissahickon Ave., Apt. D-403.
1946. Farell, David M., 1912 Spruce St.
1903. Farr, Clifford B., Bryn Mawr, Pa.
1945. Farrar, George Elbert, Jr., 528 Scott Rd., Gladwyne, Pa.
1953. Farrell, Harry L., 1930 Chestnut St. (3)
1930. Farrell, John T., Jr., 255 S. 17th St.
1935. Ferguson, Lewis Kraeer, 133 S. 36th St.
1936. Fetter, Ferdinand, 322 S. 21st St.
1945. Fetter, John S., 842 Worrell Rd., Jenkintown, Pa.
1935. Fetter, Theodore R., 255 S. 17th St.
1924. Fewell, Alexander G., 1924 Pine St.
1952. Fields, Harry, 133 S. 36th St.
1943. Finklestein, Arthur, 480 Latch's Lane, Merion, Pa.
1954. Finn, Joseph L., 7109 Rising Sun Ave. (11)

1947. First, Arthur, 1714 Spruce St.
1954. Fischer, Carl C., Germantown Professional Bldg. (44)
1945. Fiske, Frederick A., 1530 Locust St.
1952. Fitts, William T., Jr., 3400 Spruce St.
1928. Fitz-Hugh, Thomas, Jr., 2016 Delancey Pl.
1952. Flexner, Louis B., Univ. of Pa.
1928. Flick, John B., 819 Black Rock Rd., Gladwyne, Pa.
1954. Flick, John B., Jr., 330 S. 9th St. (7)
1952. Flinn, Lewis B., 503 Delaware Ave., Wilmington, Del.
1939. Flippin, Harrison F., 255 S. 17th St.
1951. Ford, Elbert S. C., 255 S. 17th St.
1954. Forster, H. Walter, Jr., 37 S. 20th St. (3)
1941. Fox, C. Calvin, 1806 Spruce St.
1906. Fraley, Frederick, 71st and City Line.
1941. Frazier, William Doane, 419 Gilpin Rd., Narberth, Pa.
1952. Freed, Herbert, 255 S. 17th St.
1953. Fried, Paul H., 1812 Spruce St. (3)
1951. Friedland, Carl K., 133 S. 36th St.
1951. Friedman, Paul Sigmund, 1422 Chestnut St.
1942. Friedman, Reuben, 1321 Spruce St.
1933. Fritch, James Scott, 269 S. 19th St.
1937. Fritz, Herbert H., Pennswood Rd., Bryn Mawr, Pa.
1953. Fruchter, Joseph M., 2104 Pine St. (3)
1940. Fry, Kenneth E., 1719 Rittenhouse Sq.
1935. Fry, Wilfred Eyles, 1930 Chestnut St.
1937. Furlong, Thomas F., Jr., Times Medical Building, Ardmore, Pa.
1954. Gambescia, Joseph M., 255 S. 17th St. (3)
1935. Gammon, Geo. D., Univ. of Pa. Hospital.
1951. Garlichs, Richard W., 216 N. Manoa Road, Havertown, Pa.
1931. Garner, Vaughn C., Germantown Professional Building.
1953. Garnet, James D., 330 S. 9th St. (7)
1950. Garvin, Eugene J., 4219 Baltimore Ave.
1953. Geckeler, Edwin O., 269 S. 19th St. (3)
1952. Gefter, William I., 366 Penn Rd., Wynewood, Pa.
1935. Geist, Donald C., 1930 Chestnut St.
1954. German, George B., 429 Cooper St., Camden, N. J.
1899. Gibbon, John H., Media, Pa.
1934. Gibbon, John H., Jr., 1025 Walnut St.
1939. Gibson, Glen Gregory, 2031 Locust St.
1944. Gifford, Edward S., Jr., 1913 Spruce St.
1954. Gilbert, Philip D., Cooper Hospital, Camden, N. J.
1954. Giletto, Basil J., 255 S. 17th St. (3)
1920. Gill, A. Bruce, 1930 Chestnut St.
1927. Gilmour, William R., 6616 Woodland Ave. (42)
1952. Gilpin, Sherman F., 3701 N. Broad St.
1949. Ginsburg, Isadore W., 3401 N. Broad St.
1931. Giordano, Anthony A. S., 1819 S. Broad St.
1954. Gislason, Gerhard J., Medical Arts Bldg. (2)
1954. Glover, Robert P., 269 S. 19th St. (3)
1954. Godfrey, Ellwood W., Princeton Hospital, Princeton, N. J.
1953. Godfrey, Lincoln, 255 S. 17th St. (3)
1945. Goldberg, Samuel J., 1723 Pine St.

1933. Goldburgh, Harold L., 1932 Spruce St.
1935. Goldsmith, N. Ralph, 1351 Tabor Rd.
1949. Gopadze, Illarion I., 1809 Delancey Pl.
1928. Gordon, Burgess L., Woman's Medical College of Pa.
1937. Gordon, William, 5345 Spruce St.
1941. Gouterman, Joseph I., 1930 Chestnut St.
1926. Grant, Francis Clark, Univ. of Pa. Hospital.
1940. Greene, Lloyd B., 136 S. 16th St.
1952. Greening, Roy R., 3400 Spruce St.
1934. Griffith, John Q., Jr., 6 N. Fredericksburg Ave., Margate, N. J.
1945. Griffiths, John E., Mermont Apartments, Bryn Mawr, Pa.
1941. Groff, Robert A., 1930 Chestnut St.
1952. Gross, Elmer R., 1402 Spruce St.
1952. Grotzinger, Paul J., Welsh & Valley Rds., Huntingdon Valley, Pa.
1952. Grove, D. Dwight, 230 N. Broad St.
1945. György, Paul, Univ. of Pa.
1935. Hadden, Samuel B., 250 S. 18th St. (3)
1951. Hafkenschiel, Joseph H., 3600 Spruce St.
1945. Hahn, George A., 255 S. 17th St.
1935. Haines, Harlan F., 134 S. State Rd., Upper Darby, Pa.
1951. Hallett, Joseph W., 1001 Medical Arts Bldg., 16th & Walnut Sts.
1939. Hamblock, Leonard C., 1632 Spruce St.
1954. Hand, B. Marvin, 269 S. 19th St. (3)
1938. Hand, John G., 1724 Pine St.
1947. Hanes, William James, 218 E. Beechtree Lane, Wayne, Pa.
1952. Harer, W. Benson, State Rd. & Rogers Ave., Bywood, Pa.
1951. Harkins, Herbert P., 1930 Chestnut St.
1932. Harris, Stanley E., 229 Maple Ave., Delanco, N. J.
1948. Harris, T. N., 2222 N. 53rd St.
1929. Harrison, Francis G., 1900 Spruce St.
1933. Harrison, William John, 135 S. 17th St.
1926. Hartmann, Fred L., 1914 Pine St.
1946. Harvey, Edith E., 406 York Rd., Jenkintown, Pa.
1947. Harvey, Rolfe Marsh, Glenmary & Houston Rds., Radnor, Pa.
1935. Haskell, Benjamin F., 1426 Spruce St.
1946. Hatfield, C. Alexander, 330 S. 9th St.
1947. Havens, Walter Paul, Jr., 300 Cherry Lane, Wynnewood, Pa.
1947. Hawthorne, Herbert Reid, 255 S. 17th St. (3)
1952. Hayllar, Benjamin L., 801 Medical Arts Bldg.
1946. Hendrickson, Frank O., 37 S. 20th St.
1953. Henny, George C., 3400 N. Broad St. (40)
1944. Herbut, Peter A., Jefferson Medical College Hospital.
1953. * Herrick, William C., Jefferson Hospital. (7)
1951. Herrman, Clinton S., 255 S. 17th St.
1954. Herron, James R., 1930 Chestnut St. (3)
1944. Hershey, J. Ivan, 935 Bowman Ave., Wynnewood, Pa.
1924. Hewson, William, 1614 Locust St.
1949. Heyl, W. Meredith, 100 W. Coulter St.
1952. Hinkson, DeHaven, 329 N. 40th St.
1924. Hirst, John C., 2d., 500 N. 20th St.
1943. Hitschler, William J., 8840 Germantown Ave.

* Military Service.

1944. Hneleski, Ignatius S., 802 S. 48th St.
1943. Hockaday, Agnes, 316 Shadeland Ave., Drexel Hill, Pa.
1939. Hodes, Philip J., Univ. of Pa. Hospital.
1947. Hodges, John H., 1025 Walnut St.
1954. Hoeffel, Joseph M., Jr., 330 S. 9th St. (7)
1948. Hoffman, George L., Jr., 133 S. 36th St.
1954. Hollander, George, 3500 Vista St. (36)
1949. Hollander, Joseph L., 36th & Spruce Sts.
1932. Hollingsworth, I. Pemberton, 411 N. Walnut St., West Chester, Pa.
1951. Hollis, Charles B., 1930 Chestnut St.
1952. Holloway, Edward E., 1739 W. Montgomery Ave.
1949. Hopkins, Henry U., Garden Court Apts., 47th & Pine Sts.
1953. Horan, Charles A., 734 N. 63rd St. (31)
1946. Horan, Gerald W., 5819 Chester Ave.
1950. Horn, Robert C., 57 Berkley Ave., Lansdowne, Pa.
1947. Horwitz, Orville, 133 S. 36th St.
1953. Hostelley, W. Vernon, 1221 Harrison St. (24)
1950. Houlihan, Carl T., 728 S. 60th St.
1944. Housel, Edmund L., 255 S. 17th St.
1928. Houser, Karl Musser, 2035 Delancey Pl.
1948. Howland, Alvin Wilcox, 255 S. 17th St.
1946. Howson, John Yeatts, 316 Lancaster Ave., Wayne, Pa.
1951. Hubbard, John P., University of Penna., School of Medicine.
1947. Huber, John Franklin, Temple University Hospital.
1937. Hughes, Joseph, 111 N. 49th St.
1939. Hughes, P. Boland, 419 Hillbrook Rd., Bryn Mawr, Pa.
1951. Hundley, J. Warren, 3818 Chestnut St.
1954. Hunsicker, William C., Jr., 255 S. 17th St. (3)
1946. Hunt, William T., Jr., 1930 Chestnut St.
1921. Hunter, Robert John, Univ. of Pa. Hospital.
1926. Husik, David N., 331 S. 46th St.
1952. Hyman, Harold L., 3401 N. Broad St.
1950. Imbriglia, Joseph E., 329 Shadeland Ave., Drexel Hill, Pa.
1952. Imperiale, C. Charles, 1331 Pine St.
1935. Ingleby, Helen, Jewish Hospital, York & Tabor Rds.
1949. Ingraham, Norman R., Jr., Stenton and Whitemarsh Ave.
1951. Isard, Harold J., Mt. Sinai Hospital, 5th & Reid Sts.
1951. Israel, Harold L., 255 S. 17th St.
1947. Israel, S. Leon, 2116 Spruce St.
1952. Iverson, Preston C., 1930 Chestnut St.
1921. Ivy, Robert H., 1930 Chestnut St.
1953. Jack, H. Wesley, 538 Cooper St., Camden, N. J. (2)
1917. Jackson, Chevalier, 3401 N. Broad St.
1932. Jackson, Chevalier L., 3401 N. Broad St.
1934. Jacobs, Maurice, 1831 Delancey Place.
1947. Jaeger, Rudolph, Jefferson Hospital.
1952. Janton, O. Henry, 269 S. 19th St.
1941. Jeffers, William A., University of Pa. Hospital.
1942. Johnson, Julian, 406 Conshohocken State Rd., Narberth, Pa.
1938. Johnson, Thomas A., 250 S. 18th St.
1952. Jonas, Karl C., 2601 Parkway.
1918. Jonas, Leon, 255 S. 17th St.

1924. Jones, Harold W., 1930 Chestnut St.
1952. Jones, Ralph, Jr., 3400 Spruce St.
1936. Kain, Thomas M., 403 Cooper St., Camden, N. J.
1948. Kaplan, Louis, 2040 Pine St.
1938. Kasper, Kelvin A., 135 S. 18th St.
1945. Katz, G. Henry, 111 N. 49th St.
1941. Kauffman, M. Luther, Medical Arts Bldg., Jenkintown, Pa.
1947. Kay, Calvin Frederick, Univ. of Pa. Hospital.
1954. Kaye, Robert, Children's Hospital, 1740 Bainbridge St. (46)
1947. Keefer, George Pfahler, 3708 Woodland Ave., Drexel Hill, Pa.
1949. Keiserman, Joseph, 5460 Baltimore Ave.
1935. Kelley, George F. J., N. E. Cor. 20th and Chestnut Sts.
1932. Kelly, Herbert T., 1900 Spruce St.
1912. Kelly, Thomas C., 105 School Lane.
1941. Kennedy, Patrick J., 32 Hampden Rd., Upper Darby, Pa.
1947. Kennedy, William Blair, Medical School, Univ. of Pa.
1948. Kern, Franklin Moore, 408 E. Wynnewood Rd., Wynnewood, Pa.
1921. Kern, Richard A., Temple University Hospital.
1935. Keyes, Baldwin L., 2031 Locust St.
1930. Kimbrough, Robert A., Jr., 807 Spruce St.
1936. King, Orville C., 330 S. 9th St.
1952. Kirshner, Jacob J., 1930 Chestnut St.
1920. Klauder, Joseph V., 1934 Spruce St.
1920. Klein, Thomas, 250 S. 18th St.
1952. Kleinbart, Morris, 1922 Pine St.
1954. Kligman, Albert M., University Hospital, 36th & Spruce Sts. (4)
1934. Kline, Oram R., 514 Cooper St., Camden, N. J.
1948. Klingensmith, Paul O., 133 S. 36th St.
1932. Klopp, John W., Gwynedd Valley, Pa.
1919. Knipe, Norman L., 514 Baird Rd., Merion, Pa.
1908. Knowles, Frank C., 423 Warick Rd., Wynnewood, Pa.
1945. Kobler, H. B., 658 N. 63rd St.
1914. Kolmer, John A., Cynwyd, Pa.
1936. Konzelmann, Frank Williamson, 12 E. Lenox St., Chevy Chase, Md.
1949. Koop, C. Everett, 1740 Bainbridge St.
1952. Kornblueh, Igho H., 1241 W. Lehigh Ave.
1941. Krall, J. Thomas, 1927 Spruce St.
1948. Kramer, David W., 2007 Pine St.
1954. Krasnoff, Sidney O., Tabor Medical Bldg. (41)
1944. Krauss, Frederick Harold, 16th & Walnut Sts.
1952. Kravitz, Charles H., 1726 Widener Pl.
1949. Kremer, David N., 1918 Pine St.
1949. Kressler, Robert J., 330 S. 9th St.
1941. Krewson, William E., 3rd, 1930 Chestnut St.
1914. Krumbhaar, Edward B., School of Medicine, Univ. of Pa.
1953. Krumperman, LeRoy W., 3401 N. Broad St. (40)
1947. Kuhlenbeck, Hartwig, Woman's Medical College.
1947. La Boccetta, Alfred Charles, 2nd and Luzerne Sts.
1952. Lachman, John W., 3401 N. Broad St.
1949. La Clair, Charles H., Jr., 1021 W. Main St., Norristown, Pa.
1952. Lafferty, Henry D., 37 S. 20th St.
1951. Lame, Edwin L., 51 N. 39th St.

1950. Lamont, Austin, 3400 Spruce St.
1946. Lampe, William T., 4207 Tyson Ave.
1952. Lang, Warren R., 255 S. 17th St.
1933. Langdon, Roy L., 5917 Greene St.
1941. Langner, Paul H., Jr., 1208 Edmonds Ave., Drexel Hill, Pa.
1945. Lansbury, John, 3401 N. Broad St.
1926. Laws, George M., 1907 Spruce St.
1936. Leaman, William G., Jr., Presidential Apts: Adams House B-909.
1950. Learner, Norman, 255 S. 17th St.
1920. Leavitt, Frederic Headley, 1527 Pine St.
1941. Leberman, Paul R., 136 S. 16th St.
1942. Lehman, James A., 255 S. 17th St.
1952. Lehman, J. Stauffer, 230 N. Broad St.
1951. Leivy, Frank E., 1321 Spruce St.
1944. Lell, William A., 255 S. 17th St.
1935. Lemmon, William T., 133 S. 36th St.
1943. Leopold, Irving H., 1930 Chestnut St.
1920. Leopold, Simon S., 255 S. 17th St.
1944. Lettiere, Anthony J., 425 E. State St., Trenton, N. J.
1933. Levering, J. Walter, Abington Memorial Hospital, Abington, Pa.
1915. Lewis, Fielding O., Providence Road, Media, Pa.
1938. Lewis, James P., 3815 Chestnut St.
1948. Lieber, Marshall M., 1025 Walnut St.
1948. Lieberman, Louis M., 923 Belmont Ave.
1940. Limberger, William A., 301 S. Church St., West Chester, Pa.
1938. Lindauer, M. August, 133 S. 36th St.
1954. Lindenmuth, Woodrow W., 330 S. 9th St. (7)
1927. Lindsey, Walter H., 810 W. Dauphin St.
1936. Lintgen, Charles, 1930 Chestnut St.
1953. Lipsius, Edward I., 1923 Spruce St. (3)
1945. Lisker, Samuel, 255 S. 17th St. (3)
1944. Livezey, Mary M., 7200 Cresheim Rd.
1936. Llewellyn, Thomas H., 910 N. 63rd St.
1907. Lodholz, Edward, The Fairfax, 43rd & Locust Sts.
1931. Loewenberg, Samuel A., 1905 Spruce St.
1933. Long, Esmond R., Henry Phipps Institute, 7th and Lombard Sts.
1949. Long, Joan Humphrey, 198 Lafayette Ave., Haddonfield, N. J.
1951. Long, Joseph P., 1930 Chestnut St.
1935. Long, William L., 2025 Walnut St.
1931. Longaker, Edwin P., 41 E. Montgomery Ave., Ardmore, Pa.
1951. Lorber, Stanley H., 3701 N. Broad St.
1942. Lownes, John B., 924 Medical Arts Bldg.
1936. Lucchesi, Pascal Francis, 601 E. Gorgas Lane.
1932. Lukens, Francis D. W., Univ. of Pa. Hospital.
1930. Lukens, Robert M., 1308 W. Hunting Park Ave.
1939. Luongo, Romeo A., 2054 Locust St.
1947. Lurie, Max B., Henry Phipps Institute, 7th and Lombard Sts.
1951. Luscombe, Herbert A., 136 S. 16th St.
1952. Lutman, Frank C., 100 W. Coulter St.
1919. Lynch, Frank B., Jr., Germantown Hosp., Penn and Chew Sts.
1950. Lynch, J. Edward, 255 S. 17th St.
1953. Lyons, John W., 255 S. 17th St. (3)

1933. McAndrews, Leo F., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1952. McCabe, Edward S., 2025 Walnut St. (3)
1932. McCahey, James F., 1534 Pine St.
1900. McCarthy, Daniel J., 2025 Walnut St.
1936. McCarthy, Patrick A., Central Medical Bldg.
1935. McClenahan, William U., 1 Summit Ave.
1931. McCloskey, Edward, 7 E. Chestnut Ave. (18)
1953. McCloskey, Joseph F., Jefferson Hospital. (7)
1935. McConnell, James W., 20th and Chestnut Sts.
1934. McCouch, Grayson P., Medical School, Univ. of Pa.
1938. McCrea, Lowrain E., 1930 Chestnut St.
1954. McCrory, Wallace W., Children's Hospital, 1740 Bainbridge St. (46)
1937. McCutcheon, Morton, Cambridge Apts.
1942. McDonald, P. Robb, 1930 Chestnut St.
1953. McDonnell, William V., 1025 Walnut St. (7)
1952. McElroy, Robert C., 133 S. 36th St.
1950. McFadden, William M., 1187 E. Washington Lane.
1949. McGavic, John S., 601 Montgomery Ave., Bryn Mawr, Pa.
1945. McGee, Lemuel Clyde, Hercules Powder Company, Wilmington, Del.
1954. McGehee, Edward H., 15 E. Highland Ave. (18)
1952. McGlade, Thomas H., 719 Cooper St., Camden, N. J.
1933. McLaughlin, James S., 330 S. 9th St.
1924. McMillan, Thomas M., 2044 Locust St.
1924. McPhedran, F. Maurice, Germantown Hosp., Penn and Chew Sts.
1954. MacFadyen, Bruce V., 135 S. 18th St. (3)
1943. Macfarlan, Douglas, 1805 Chestnut St.
1932. Macfarlane, Catharine, 136 S. 16th St.
1947. Machella, Thomas E., Univ. of Pa. Hospital.
1950. Mackmull, Gulden, Germantown Professional Building.
1949. MacNeal, Perry Scott, 330 S. 9th St.
1939. Macneill, Norman N., 5807 Chew St.
1951. Mac Neish, W. J., Medical Arts Bldg., 16th & Walnut Sts.
1935. Maeder, LeRoy M. A., 1910 Rittenhouse Sq.
1952. Mahoney, J. Francis, 250 S. 18th St.
1942. Manges, Lewis C., Jr., 319 S. 16th St.
1954. Manges, Willis E., Methodist Hospital, Broad & Wolf Sts. (48)
1936. Mann, Bernard, 2019 Pine St.
1953. Marbach, A. Herbert, 255 S. 17th St. (3)
1948. Marden, Philip Ayer, 1912 Spruce St.
1937. Margolies, Alexander, 1351 Tabor Rd.
1950. Mark, George E., 3401 N. Broad St.
1950. Marshall, E. Wayne, Jr., 1520 Spruce St.
1941. Martin, James R., 1025 Walnut St. (7)
1951. Martin, William L., Hahnemann Hospital.
1952. Martucci, Albert A., 1460 E. Cheltenham Ave.
1953. Marx, Halvey E., 282 N. Lansdowne Ave., Lansdowne, Pa.
1953. Massey, Franklin C., 136 S. 16th St. (2)
1939. May, Hans, 255 S. 17th St.
1951. Mayock, Robert L., 3600 Spruce St. (4)
1934. Mecray, Paul M., 405 Cooper St., Camden, N. J.
1952. Mecray, Paul, Jr., 405 Loucroft Ave., Haddonfield, N. J.
1951. Medinger, Frederick G., 255 S. 17th St.

1941. Mendell, Theodore H., 2023 Spruce St.
1951. Mendelssohn, Edwin, 255 S. 17th St.
1949. Menkin, Valy, 3401 N. Broad St.
1943. Meranze, David R., 1031 Lakeside Ave.
1937. Meyer, George Phillip, 410 Haddon Ave., Camden, N. J.
1935. Miller, Ford A., 4016 Chestnut St.
1946. Miller, Franklin R., Jefferson Medical College.
1939. Miller, Malcolm W., 255 S. 17th St.
1939. Miller, Merle M., 6013 Greene St.
1932. Miller, M. Valentine, 114 W. Phil-Ellena St.
1921. Miller, T. Grier, 133 S. 36th St.
1952. Minehart, John R., 4821 Germantown Ave.
1952. Mintz, S. S., 1429 S. 5th St.
1937. Missett, Joseph Vincent, Jr., 2031 Locust St.
1904. Mitchell, Charles Franklin, 2003 Pine St.
1950. Mitchell, John McK., Medical School, Univ. of Pa.
1952. Mitchell, Robert McNair, 330 S. 9th St.
1948. Mogavero, Francesco, 1930 Chestnut St.
1932. Mohler, Roy W., 1806 Spruce St.
1936. Montgomery, Hugh, 119 Glenn Road, Ardmore, Pa.
1936. Montgomery, John B., 1930 Chestnut St.
1932. Montgomery, Thaddeus L., 2031 Locust St.
1951. Moore, Edward J., 204 Meeting House Lane, Merion, Pa.
1935. Moore, John Royal, 3401 N. Broad St.
1947. Moore, Matthew Thibaud, 1813 Delancey Pl.
1924. Moorhead, Stirling W., 1523 Pine St.
1936. Morgan, David R., Jefferson Medical College.
1893. Morris, Elliston J., 439 Midland Ave., St. Davids, Del. Co., Pa.
1944. Morris, Harold H., Villa Nova, Pa.
1945. Morris, I. Paul, 1939 Cheltenham Ave.
1941. Mucklé, Craig Wright, 330 S. 9th St. (7)
1929. Mudd, Stuart, Department of Bacteriology, Medical School, Univ. of Pa.
1949. Mulholland, Stanford W., 22nd & Parkway.
1935. Mullen, Carroll Richard, 2025 Locust St.
1934. Mullen, Edward A., 472 Roxborough Ave.
1930. Murphy, Douglas P., Univ. of Pa. Hospital.
1953. Murphy, Edward J., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1951. Myers, David, 304 S. 19th St.
1945. Naide, Meyer, 2034 Spruce St.
1951. Naidoff, David, 3500 Tudor St. (36)
1950. Nardone, Anthony A., 912 S. 49th St.
1950. Neefe, John R., 2021 Delancey Pl.
1948. Neese, Paul H., 17 Derwen Road, Cynwyd, Pa.
1936. Nelson, Guy M., 255 S. 17th St.
1943. Nelson, Waldo E., 615 Moreno Rd., Narberth, Pa.
1905. Newcomet, William S., 3501 Baring St.
1938. Newton, Zachariah B., 601 E. Sedgwick St.
1935. Nicholson, Jesse Thompson, Pennsylvania Hospital.
1950. Nixon, Norman, 111 N. 49th St.
1947. Noone, Ernest L., 4501 Cedar Lane, Drexel Hill, Pa.
1905. Norris, Charles C., Darby and Goshen Roads, Bryn Mawr, Pa.
1954. Norris, Charles M., 3401 N. Broad St. (40)

1938. Norris, Robert F., 513 Wynnewood Ave., Wynnewood, Pa.
1947. O'Keefe, John J., 255 South 17th St.
1954. Olsen, Axel K., 230 N. Broad St. (2)
1913. O'Neal, Alexander Hay, St. Davids, Pa.
1949. O'Neill, James F., 140 Roslyn Ave., Glenside, Pa.
1954. O'Neill, Thomas J. E., 269 S. 19th St. (3)
1947. Ornsteen, A. M., 2007 Delancey Pl.
1947. Ornston, Darius Gray, 36 Carpenter Lane.
1936. Orr, Theodore E., 1930 Chestnut St.
1913. Outerbridge, George W., 1927 Spruce St.
1915. Owen, Hubley R., 1505 Walnut St.
1949. Padis, Nicholas, 255 S. 17th St.
1954. Palmer, Louis H., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1909. Parish, Benjamin Dores, 1927 Spruce St.
1945. Park, Felix Roman, Medical Arts Bldg., Tulsa, Okla.
1940. Parker, Alan P., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1948. Parkhurst, Leonard Woods, 330 S. 9th St.
1944. Paschkis, Karl E., Jefferson Medical College.
1952. Paxson, Newlin F., 250 S. 18th St.
1932. Payne, Franklin L., Univ. of Pa. Hospital.
1954. Pearce, Alexander E., 1420 Race St. (2)
1943. Pearson, Gerald H. J., Presidential Apts.—Adams House.
1954. Pearson, Manuel M., 111 N. 49th St. (39)
1952. Peck, Roy I., 3400 Spruce St.
1930. Pendergrass, Eugene P., Univ. of Pa. Hospital.
1953. Penneys, Raymond, University Hospital
1914. Pepper, O. H. Perry, Ithan, Pa.
1916. Percival, Milton Fraser, 2332 S. Broad St.
1942. Perkins, William Harvey, 1025 Walnut St.
1946. Perloff, William Harry, 3521 N. Broad St.
1951. Perri, Angelo M., 814 Federal St.
1953. Persky, Abram H., 1737 Chestnut St. (3)
1940. Pessel, Johannes F., 224 West State St., Trenton, N. J.
1952. Peters, Michael, 262 W. Broad St., Telford, Pa.
1940. Pettit, Horace, Times Medical Bldg., Ardmore, Pa.
1949. Pettit, Mary DeWitt, 1930 Spruce St.
1905. Pfahler, George E., 1930 Chestnut St.
1915. Pfeiffer, Damon B., Meadowbrook, Pa.
1946. Pfeiffer, Mildred C. J., 358 Valley Rd., Merion, Pa.
1935. Phillips, Arthur W., 3904 Walnut St.
1911. Piersol, George Morris, 308 Kent Rd., Wynnewood, Pa.
1948. Pierson, Daniel B., Jr., 1830 Delancey St.
1933. Pillsbury, Donald M., Univ. of Pa. Hospital.
1950. Pincus, Irwin J., 269 S. 19th St.
1951. Poinsard, Paul J., 2031 Locust St.
1937. Polk, David Stewart, Rosemont, Pa.
1953. Porreca, George A., 1912 Spruce St. (3)
1932. Porter, Roland De Lance, Abington, Pa.
1953. Posey, William C., Jr., 600 Suburban Square Bldg., Ardmore, Pa.
1951. Post, Joseph W., 1930 Chestnut St.
1951. Pote, Harry H., 4032 Walnut St.
1949. Pratt, Gerald E., 3009 Frankford Ave.

1951. Pressman, Robert S., 269 S. 19th St.
1947. Prickett, John A., Warrington, Bucks County, Pa.
1954. Prince, Leon N., 2025 Spruce St. (3)
1931. Pryor, Charles Allen, 255 S. 17th St.
1952. Pugh, James E., 614 Church Lane, Yeadon, Pa.
1947. Putney, Floyd Johnson, 1719 Rittenhouse Sq.
1943. Radbill, Samuel X., 7043 Elmwood Ave.
1953. Radbill, Sidney G., 37 S. 20th St. (3)
1945. Rakoff, Abraham Edward, 269 S. 19th St.
1953. Ralston, Edgar L., 3400 Spruce St. (4)
1931. Ramsey, Frank M., 620 E. Willow Grove Ave.
1953. Ranieri, Tito A., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1941. Rankin, Charles A., Ludlow & Heather Rd., Upper Darby, Pa.
1946. Rapoport, Milton, Children's Hospital, 1740 Bainbridge St.
1951. Rathmell, Thomas K., 446 Bellevue Ave., Trenton, N. J.
1926. Ravdin, I. S., Univ. of Pa. Hospital.
1954. Reagan, Lindley B., 175 Madison Ave., Mt. Holly, N. J.
1928. Reese, Warren S., 2118 Locust St.
1925. Reeves, Rufus S., Presidential Apts., A-910.
1920. Rehfuss, Martin E., 131 St. George's Rd., Ardmore, Pa.
1921. Reiff, E. Paul, 1927 Spruce St.
1919. Reimann, Stanley P., 703 W. Phil-Ellena St.
1951. Rentschler, Laurence B., 5800 Ridge Ave.
1945. Rhoads, Jonathan E., Univ. of Pa. Hospital.
1936. Richards, James L., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1951. Richardson, Fred Mac D., 160 Carpenter Lane.
1919. Richardson, Russell, Phila. Tuberculosis Sanitorium #4, Corinthian & Girard Aves.
1951. Riegel, Donald, 5110 Chester Ave.
1942. Riggs, Helena E., 150 Hewitt Rd., Wyncote, Pa.
1936. Ritter, Joseph A., 2405 N. 54th St.
1932. Robbins, Frederick R., 317 Milbank Rd., Bryn Mawr, Pa.
1952. Robbins, Robert, 3401 N. Broad St.
1954. Roberts, Brooke, 3400 Spruce St. (4)
1939. Roberts, Ella, 133 S. 36th St.
1954. Roberts, Norbert J., Penna. Railroad, 1617 Penna. Blvd. (3)
1899. Roberts, Walter, 335 S. Camac St. (7)
1932. Robertson, Harold F., 2118 Pine St.
1954. Robertson, Hugh, 255 S. 17th St. (3)
1903. Robertson, William Egbert, 2118 Pine St.
1938. Roche, Philip Q., 255 S. 17th St.
1912. Rodman, John Stewart, 524 Manor Rd., Wynnewood, Pa.
1954. Roesler, Elizabeth Mertens-, 224 W. School House La. (44)
1947. Rogers, Arthur Merriam, Univ. of Pa. Hosp. (4)
1934. Rogers, Harry L., 255 S. 17th St.
1951. Ronis, Bernard J., 2106 Spruce St.
1948. Roscoe, Constantine R., 7226 Castor Ave.
1928. Rose, Edward, 426 Owen Rd., Wynnewood, Pa.
1936. Rose, Elizabeth Kirk, 426 Owen Rd., Wynnewood, Pa.
1952. Rose, S. Brandt, Chestnut Hill Hospital.
1946. Rosemond, George Parrott, Temple University, Broad & Ontario Sts.
1948. Rothman, Maurice M., 1727 Spruce St.
1932. Rothrock, Harry A., West Chester, Pa.

1951. Rouse, Jr., George P., 2031 Locust St.
1952. Roxby, Bruce S., 5501 Greene St.
1937. Roxby, John B., 113 Yale Ave., Swarthmore, Pa.
1949. Royster, Henry P., 3400 Spruce St.
1941. Royster, Jr., Hubert A., The Mermont, Bryn Mawr, Pa.
1952. Rubin, I. Edward, 255 S. 17th St. (3)
1933. Rudolphy, Jay Besson, 230 S. 21st St.
1946. Rupp, Charles, 133 S. 36th St.
1947. Rush, Alexander, 330 South 9th St.
1954. Ruth, Henry S., 225 Cheswold La., Haverford, Pa.
1945. Rynes, Samuel E., 334 S. 21st St.
1952. Sain, Fletcher D., Abington Memorial Hospital, Abington, Pa.
1952. Salner, Nathan P., 6812 Castor Ave. (24)
1952. Saltzman, Maurice, 1923 Spruce St.
1944. Sampson, David Alan, 726 Braeburn Lane, Penn Valley, Narberth, Pa.
1954. Sampson, Martin C., 418 S. 47th St. (43)
1936. Sands, Joseph Evans, Rosemont, Pa.
1950. Sarner, Joseph B., 269 S. 19th St. (3)
1949. Saul, Leon J., Highland Ave., Media, Pa.
1908. Sautter, Albert C., Germantown Professional Bldg.
1954. Savacool, J. Woodrow, 146 W. Tulpehocken St. (44)
1947. Saÿen, John J., 506 Montgomery Ave., Haverford, Pa.
1948. Scarano, Joseph Albert, 1432 S. Broad St.
1917. Schaeffer, J. Parsons, Daniel Baugh Institute, 307 S. 11th St.
1929. Scheffey, Lewis C., 255 S. 17th St.
1942. Scheie, Harold G., 313 S. 17th St.
1929. Schenck, Harry P., 1235 Wyngate Rd., Wynnewood, Pa.
1945. Schlezinger, Nathan S., 255 S. 17th St.
1917. Schnabel, Truman G., 1704 Pine St.
1917. Schoff, Charles H., Media, Pa.
1952. Schulz, Norbert J., 1901 Walnut St.
1921. Schumann, Edward A., 8815 Germantown Ave. (18)
1950. Schumann, Francis N., 8811 Germantown Ave.
1948. Schwarz, Gabriel A., 1711 Rittenhouse Sq.
1930. Scott, John Porter, Children's Hospital, 1740 Bainbridge St.
1950. Scott, Michael, 255 S. 17th St.
1940. Scott, T. F. McNair, Children's Hospital, 1740 Bainbridge St.
1952. Seifer, Arthur F., 3401 N. Broad St.
1954. Seifter, Joseph, 900 N. Broad St. (30)
1951. Seitchik, Joseph N., 1417 Race St., Hahnemann Medical College Annex.
1952. Semisch, Charles W., III, 5329 Rising Sun Ave.
1951. Shaffer, Bertram, 1825 Pine St.
1924. Shallow, Thomas A., 1611 Spruce St.
1950. Sharp, Reuben L., 719 Cooper St., Camden, N. J.
1928. Sharpless, Frederick C., Beach Haven, N. J.
1948. Shay, Harry, 3400 N. Broad St.
1954. Shelley, Walter B., University Hospital, 36th & Spruce Sts. (4)
1946. Shepherd, Samuel Garfield, 2039 Pine St.
1932. Sheridan, Joyce T., 412 W. Durham St.
1936. Shipman, James Shelby, 255 S. 17th St.
1935. Shoemaker, Robert, 3rd, 68 Byberry Rd., Hatboro, Pa.
1951. Shorey, Winston K., 185 Meredith Ave., Rosemont, Pa.

1946. Shoup, George Daniel, 121 W. Walnut Lane. (44)
1952. Shuman, Charles R., 3401 N. Broad St.
1936. Shuster, Benjamin H., 1824 Pine St.
1949. Sidlick, David M., 255 S. 17th St.
1941. Silcox, Louis E., 255 S. 17th St.
1954. Singmaster, Laurence, 255 S. 17th St. (3)
1952. Skromak, Stanley J., 5108 Torresdale Ave.
1929. Smith, Austin T., 1830 Spruce St.
1933. Smith, Lauren Howe, 111 N. 49th St.
1952. Smith, Richard T., 330 S. 9th St.
1927. Smyth, Calvin Mason, Abington Memorial Hospital, Abington, Pa.
1951. Snape, William J., 573 Stevens St., Camden, N. J.
1938. Snodgrass, L. E., 709 Walnut St. (6)
1953. Snyder, G. Gordon, Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1935. Sokoloff, Martin J., 255 S. 17th St.
1940. Soloff, Louis A., 255 S. 17th St.
1950. Somerville, William J., 2022 Locust St.
1935. Sommer, George N. J., 120 W. State St., Trenton, N. J.
1944. Sommer, George N. J., Jr., 120 W. State St., Trenton, N. J.
1952. Sones, Maurice, Mt. Airy Medical Bldg.
1951. Sonneborn, Duane G., 1200 W. Erie Ave.
1928. Spaeth, Edmund B., 1930 Chestnut St.
1937. Spangler, John Luther, Devon, Pa.
1935. Spiegel, Ernest, 6807 Lawnton Ave., Oak Lane.
1944. Stadie, William C., University Hospital.
1927. Starr, Isaac, 505 Cresheim Valley Rd.
1952. Stauffer, Herbert M., 3401 N. Broad St.
1952. Stayman, Joseph W., Jr., Germantown Hospital.
1945. Stecher, H. Armin, 1510 Darby Rd., Havertown, Pa.
1953. Steele, Brandt F., 1640 Pine St. (3)
1952. Steele, Eleanor A., 1640 Pine St.
1952. Steiger, William A., 3401 N. Broad St.
1946. Stein, Irvin, 1936 Spruce St.
1953. Stein, Raymond O., 1936 Spruce St. (3)
1936. Steinfield, Edward, N. E. Cor. 18th and Chestnut Sts.
1942. Stengel, Alfred, Jr., 160 Hodge Rd., Princeton, N. J.
1951. Sterling, Julian A., 255 S. 17th St.
1948. Stevens, Lloyd W., 133 S. 36th St.
1941. Stewart, Winifred B., 1930 Spruce St.
1949. Stockwell, Eunice L., 2018 Pine St.
1925. Stokes, John H., 4228 Spruce St.
1928. Stokes, Joseph, Jr., Children's Hospital, 1740 Bainbridge St.
1943. Stokes, S. Emlen, 129 Chester Ave., Moorestown, N. J.
1954. Stone, Hrant H., E. Shawmont Ave. (28)
1952. Stoner, Emery K., 222 E. Mt. Pleasant Ave.
1953. Strawbridge, Rendall R., 269 S. 19th St. (3)
1923. Strecker, Edward A., 111 N. 49th St.
1953. Stroud, Morris W., 3rd, Highland View Hosp., Cleveland 22, Ohio.
1923. Stroud, William Daniel, 1011 Clinton St.
1937. Strumia, Max M., Penn Valley, Narberth, Pa.
1937. Sturgis, Margaret C., 349 Wistar Rd., Wynnewood, Pa.
1927. Sturgis, Samuel Booth, 349 Wistar Rd., Wynnewood, Pa.

1934. Summey, Thomas J., Burlington County Hosp., Mt. Holly, N. J.
1930. Sunderman, F. William, 6627 Greene St.
1936. Surver, James Miller, 1015 Walnut St.
1954. Sussman, Marcel S., 101 S. 20th St. (3)
1928. Swartley, William B., 6002 Greene St.
1944. Swenson, Paul C., Jefferson Hospital.
1948. Tait, Edwin Forbes, 1324 Main St., Norristown, Pa.
1943. Tassman, Isaac S., 136 S. 16th St.
1946. Tauber, Robert, 2019 Walnut St.
1952. Taylor, Ann Gray, 6364 Germantown Ave.
1931. Taylor, Norman H., 100 W. Evergreen Ave.
1951. Theodos, Peter A., 1930 Chestnut St.
1946. Thomas, Carmen C., 1930 Chestnut St.
1928. Thomas, J. Earl, Drexel Hill, Pa.
1952. Thompson, Charles M., 255 S. 17th St.
1927. Thorington, J. Monroe, 2031 Chestnut St.
1936. Thornton, Mary Bickings-, 2703 West Somerset St.
1936. Thorp, Francis Quicksall, 4900 Penn St.
1936. Thudium, William J., 136 S. 16th St.
1954. Tindall, Dorothy D., 37 S. 20th St. (3)
1935. Tocantins, Leandro Maués, 1025 Walnut St.
1945. Toland, Joseph J., Jr., 1241 W. Lehigh Ave.
1935. Toland, Owen J., Episcopal Hospital, Front and Lehigh Ave.
1952. Tompkins, Winslow T., 330 S. 9th St.
1952. Tondreau, Roderick L., 227 Crosshill Rd., Penn Wynne, Pa.
1953. Topping, Norman H., 3446 Walnut St. (4)
1949. Tornay, Anthony S., 37 S. 20th St.
1945. Tourish, William J., 250 S. 17th St.
1949. Town, Arno E., 255 S. 17th St.
1936. Towson, Charles Emory, Germantown Professional Bldg.
1908. Tracy, Stephen E., Old Arch Rd., Norristown, Pa.
1954. Trommer, Philip R., 258 S. 18th St. (3)
1953. Tropea, Frank, Jr., 269 S. 19th St. (3)
1947. Trueman, Robert H., 1930 Chestnut St.
1954. Truitt, R. Marshall, 740 West View St. (19)
1926. Tucker, Gabriel, 250 S. 18th St.
1938. Tuft, Louis, 1530 Locust St.
1933. Tumen, Henry J., 1900 Rittenhouse Sq.
1938. Turman, Christopher M., Wyncote, Pa.
1923. Turner, Creighton H., 1731 Pine St.
1954. Turner, Linton W., 3401 N. Broad St. (40)
1952. Twining, H. Earle, 2026 Delancey St.
1929. Tyson, Ralph M., 255 S. 17th St.
1937. Uhle, Charles A. W., 255 S. 17th St.
1953. Ulin, Alexander W., 230 N. Broad St. (7)
1907. Ullom, Josephus T., Carpenter and Quincy Sts.
1950. Valdes-Dapena, Antonio, 40 Lokesley Rd., Merion, Pa.
1937. Vander Veer, Joseph B., 330 S. 9th St.
1937. Van Loon, Emily Lois, 1930 Chestnut St.
1933. Vastine, Jacob H., 2nd, 136 S. 16th St.
1947. Vastine, Mary F., Woman's Medical College of Pa.
1952. Vischer, Thomas J., 5903 Greene St.

1940. Voegelin, Adrian W., Germantown Professional Bldg.
1941. Vogel, Stoughton R., 151 W. Tulpehocken St.
1903. Wadsworth, William S., 4632 Hazel Ave.
1927. Wagers, Arthur J., 1429 Spruce St.
1949. Wagner, Frederick B., Jr., 251 S. 41st St.
1949. Wagner, Joseph A., 2720 Darby Rd., Havertown, Pa.
1928. Wagoner, George W., Medical Bldg., Bryn Mawr, Pa.
1954. Wainer, Amos S., 1621 Spruce St. (2)
1938. Waldman, Joseph, 404 Meadowbrook Lane.
1952. Walker, James M., 3400 Spruce St.
1906. Walker, John K., 139 Little Lane, Haverford, Pa.
1907. Walker, Warren, 511 Lynmere Rd., Bryn Mawr, Pa.
1932. Walkling, Adolph A., 136 S. 16th St.
1932. Watt, Charles C., Jr., 100 W. Coulter St.
1954. Waugh, Elizabeth S., 5910 Greene St. (44)
1933. Waygood, James J., 736 Westview St. (19)
1952. Weaver, Harry S., Jr., 37 S. 20th St.
1941. Weaver, Ruth H., 2601 Parkway.
1953. Weber, Lennard L., 255 S. 17th St. (3)
1930. Weeder, S. Dana, 250 W. Tulpehocken St.
1920. Weidman, Fred D., 20 Tenby Rd., Havertown, Pa.
1954. Weiner, Louis H., 4025 Girard Ave. (4)
1952. Weinstein, George L., 255 S. 17th St.
1954. Weinstock, Horace L., 329 S. 18th St. (3)
1933. Weiss, Benjamin P., The Lenox, 13th and Spruce Sts.
1923. Weiss, Edward, 269 S. 19th St.
1950. Weiss, Sidney, 1930 Chestnut St.
1951. Welty, Jack W., Montgomery Ave. & Owen Rd., Wynnewood, Pa.
1935. Whelan, G. L., 2100 Walnut St.
1921. Whitaker, William, 4645 Oakland St.
1936. White, Ellen Pawling Corson-, Gladwyne, Pa.
1925. Widmann, Bernard P., 250 S. 18th St.
1954. Wieder, Henry S., Jr., 330 S. 9th St. (7)
1936. Wilder, Theodore S., 6013 Greene St.
1935. Willard, John Harrington, 344 S. 15th St.
1939. Willauer, George, 6129 Greene St.
1907. Williams, Carl, School Lane and Greene St.
1937. Williams, John C., 6370 Germantown Ave.
1920. Williams, Philip F., 355 Bala Ave., Bala-Cynwyd, Pa.
1950. Williams, R. G., Medical School, Univ. of Pa.
1927. Williamson, Ernest G., 6353 Woodbine Ave.
1949. Willson, J. Robert, 3401 N. Broad St.
1921. Wilson, George, 133 S. 36th St.
1945. Wilson, John F., 2013 Delancey Pl.
1953. Wilson, Julius L., Henry Phipps Institute, 7th & Lombard Sts. (47)
1937. Wilson, Ross B., 1832 Spruce St. (3)
1949. Wilson, William W., 133 S. 36th St.
1948. Winkelman, Nathaniel W., 1911 Spruce St.
1948. Winston, Julius, 5839 Chester Ave.
1941. Wirts, C. Wilmer, 2017 Delancey St.
1904. Wister, James W., 5430 Germantown Ave.
1953. Wohl, George T., 1727 Pine St. (3)

1933. Wohl, Michael G., 1727 Pine St.
1944. Wolf, Lewis R., 3474 Frankford Ave.
1918. Wolferth, Charles C., 133 S. 36th St.
1942. Wolman, Irving J., 7607 Woodlawn Ave. (26)
1893. Wood, Alfred C., 2035 Walnut St.
1950. Wood, Dorothy D., 2035 Walnut St.
1932. Wood, Francis C., 212 Laurel Lane, Haverford, Pa.
1903. Wood, Horatio C., Jr., 319 S. 41st St.
1944. Wood, H. Curtis, Jr., Skippack Pk., Whitemarsh, Pa.
1953. Woodruff, Marston T., 4940 Penn St. (24)
1928. Wright, Carroll S., 1402 Spruce St.
1937. Yaskin, Joseph C., 1832 Spruce St.
1943. Yawger, Nathaniel S., Exeter Rd., Haverford, Pa.
1921. Ylvisaker, Lauritz S., P.O. Box 268, Bryn Mawr, Pa.
1941. Young, Barton R., Germantown Hospital.
1953. Zarafonetis, Chris, 3401 N. Broad St. (40)
1946. Zeigerman, Joseph H., 1836 Delancey St.
1894. Zentmayer, William, 265 Forrest Rd., Merion, Pa.
1952. Zillessen, Frederick O., Jeanes Hospital.
1949. Zintl, William J., Upper Darby, Pa.
1933. Zulick, J. Donald, Abington Memorial Hospital, Abington, Pa.

Associate Fellows

ELECTED

1951. Shorey, Jeannette McC., 185 Meredith Ave., Rosemont, Pa.
1952. Talbot, Timothy R., Jr., University Hospital, 36th & Spruce Sts.

Non-Resident Fellows

ELECTED

1912. Addison, William H. F., 286 East Sidney Avenue, Mt. Vernon, N. Y.
1941. Aronson, Roland S., Medical Laboratory, Ft. McPherson, Ga.
1934. Bank, Joseph, 800 N. First Ave., Phoenix, Arizona.
1932. Behney, Charles A., 4 S. Dunlap St., Memphis 3, Tenn.
1949. Bixby, Edward W., 61 W. Ross St., Wilkes-Barre, Pa.
1937. Braceland, Francis J., The Institute of Living, 200 Retreat Av., Hartford, Conn.
1948. *Brown, Robert B., U. S. Naval Hospital, Bethesda, Md.
1908. Cadbury, William W., 274 W. Main St., Moorestown, N. J.
1936. Camero, Anthony R., 657 S. Westlake Ave., Los Angeles, Cal.
1941. Cheleden, John, 133 Broadway, Daytona Beach, Fla.
1930. Clarke, Francis Mann, 116 New St., New Brunswick, N. J.
1926. Clerf, Louis H., 5575–8th Ave., North, St. Petersburg, Fla.
1930. Cottrell, James E., Kennedy Veteran's Administration Hospital, Richmond 19, Va.
1940. Crowe, Aldrich C., 1208 Ocean Ave., Ocean City, N. J.
1947. Cutler, Norman L., 1300 Harrison St., Wilmington, Del.
1941. *Cuttle, Tracy D., U. S. Naval Hospital, F.P.O., San Francisco, Cal.
1941. Dixon, Harold M., 1624 N. Harrison St., Little Rock, Ark.
1897. Dorland, W. A. Newman, 113 S. Boulevard, Tampa, Fla.
1951. Ellis, Mackinnon, Mountain Home Veteran's Hospital, Mountain Home, Tenn.

*Military Service.

1951. Ervin, Carl E., 240 North Third Street, Harrisburg, Pa.
1944. Estes, W. L., Jr., Bethlehem, Pa.
1952. Faller, Constantine P., 127 State St., Harrisburg, Pa.
1940. Forrester, James S., Harrisburg Polyclinic Hospital, Harrisburg, Pa.
1946. Forster, Francis M., Georgetown University Hospital, Washington, D. C.
1947. Gaskill, Herbert S., 250 Ash St., Denver, Colorado.
1913. Gates, Nathaniel, 10 Peterboro, Detroit, Mich.
1931. Gilman, Robert Louis, Cheyney, Pa.
1947. Grady, Hugh G., Armed Forces Institute, Washington, D. C.
1952. Grieco, Reynold M., 2 W. 4th St., Williamsport, Pa.
1933. Gruber, Charles M., School of Medicine, College of Medical Evangelists, Loma Linda, Calif.
1936. Guthrie, Donald, 118 S. Wilbur Ave., Sayre, Pa.
1936. Hatch, Lerleen Clement, 2184 Ayers Ave., Akron, Ohio.
1928. Hayman, Joseph Marchant, Jr., Tufts College Medical School, Boston, Mass.
1933. Hitzrot, Lewis H., Medical Director, Mercersburg Academy, Mercersburg, Pa.
1938. Howell, John C., 1104 Logan Ave., Tyrone, Pa.
1936. Hughes, Brady A., 312 Euclid Ave., Mt. Brook, Birmingham, Ala.
1953. Imber, Irving, 420 Walnut St., Reading, Pa.
1947. Kelchner, Clyde H., 1125 Turner St., Allentown, Pa.
1942. Kneedler, William H., 609 N. Statesville Rd., Davidson, N. C.
1944. LaMotte, William O., Medical Arts Building, Wilmington, Del.
1954. LaMotte, William O., Jr., 601 Delaware Ave., Wilmington, Del.
1952. Levan, John B., 401 Oley St., Reading, Pa.
1949. Lhamon, William T., Baylor University College of Medicine, Houston, Tex.
1954. Light, John J. B., 25 N. 9th St., Lebanon, Pa.
1948. Livingood, Clarence S., Henry Ford Hospital, Detroit 2, Mich.
1948. McCall, Milton L., Louisiana State Univ., New Orleans, La.
1937. McGuinness, Aims C., 1427 I St., N.W., Washington 5, D. C.
1948. McLaughlin, John T., 1252 S. Central Ave., Glendale, Calif.
1949. Manlove, Francis R., 6015 E. 17th Ave., Denver, Colo.
1953. Margolies, Michael, 567 E. Chestnut St., Coatesville, Pa.
1935. Mason, James B., 40 E. Erie St., Chicago 11, Ill.
1935. Matthews, Robert A., 1542 Tulane Ave., New Orleans, La.
1932. Meade, Richard H., Jr., 750 San Jose Dr., Grand Rapids, Mich.
1936. Middleton, William Shainline, 2114 Adams St., Madison, Wisconsin.
1928. Moon, Virgil H., Univ. of Miami, Coral Gables, Fla.
1949. Motley, Hurley L., 1212 Shatto St., Los Angeles, Calif.
1937. Nicholson, Samuel T., 2d., 642 High St., Pottstown, Pa.
1941. Nisbet, Verner, 714 Queens Rd., Charlotte 7, N. C.
1905. Norris, George W., Dimock, Pa.
1952. Nutt, John B., 416 Pine St., Williamsport, Pa.
1926. Paul, John Rodman, Dept. Preventive Medicine, Yale University, New Haven, Conn.
1947. Pearce, Louise, Trevenna Farms, Belle Mead, N. J.
1922. Pleasants, Henry, West Chester, Pa.
1953. Raffensperger, Edward C., 2039 N. 2nd St., Harrisburg, Pa.
1938. Read, Hilton S., 5407 Atlantic Ave., Atlantic City, N. J.
1936. Reisinger, John A., 901 20th St., N.W., Washington, D. C.
1907. Royer, B. Franklin, 429 E. Baltimore St., Greencastle, Pa.
1953. Scanlan, Robert L., St. Vincent's Hospital, 2131 W. 3rd St., Los Angeles 57, Calif.
1945. Schell, James F., Veterans Hospital, Wilmington, Del.
1928. Schofield, Frederick S., Veteran's Admin. Hospital, Beckley, W. Va.
1913. de Schweinitz, George L., 203 E. Broad St., Bethlehem, Pa.

1941. Shands, Alfred R., Jr., Alfred I. duPont Institute, Rockland Rd., Wilmington, Del.
1908. Shannon, Charles E. G., 9 Park St., Waterville, Maine.
1943. Shewbrooks, Daniel N., The Acacia Mutual Life Ins. Co., Washington, D. C.
1950. Shiffer, Paul H., 111 N. 7th St., Stroudsburg, Pa.
1932. Siegel, Alvin Erdreich, Medical Arts Building, Macon, Ga.
1933. Smelzer, Donald C., Lancaster General Hospital, Lancaster, Pa.
1954. Smith, Charles W., 121 State St., Harrisburg, Pa.
1929. Sponsler, Marshall B., 103 Lansdowne Road, DeWitt, N. Y.
1934. Stewart, Sloan G., Pacific and North Carolina Avenues, Atlantic City, N. J.
1931. Stiles, Merritt H., 820 S. McClellan St., Spokane, Wash.
1952. Sweeney, Francis X., St. Joseph's Hosp., Tacoma 3, Wash.
1942. Thompson, Wesley D., 18 N. Main St., Lewistown, Pa.
1941. Tompkins, Pendleton, 450 Sutter St., San Francisco, California.
1950. Ullery, John C., Ohio State University, Columbus, Ohio.
1913. Vail, William Penn, Blairstown, N. J.
1912. Vaux, Norris W., Glenmore Farms, Glen Moore, Pa.
1897. Veasey, Clarence A., 1118 W. 9th Ave., Spokane 9, Wash.
1931. Walker, Herschel Carey, 320 Park Ave., New York City, N. Y.
1914. Willard, De Forrest P., 38 Nyack Ave., Lansdowne, Pa.
1952. Wood, Horatio C., III, 4309 Prospect Rd., Peoria, Ill.
1947. Zintel, Harold A., St. Luke's Hospital, Amsterdam Ave. & 113th St., New York 25, N. Y.

Honorary Fellows

Limited to Fifty, of Whom Twenty May Be Foreigners

American

ELECTED

1917. Miner, Charles Howard, b.s., m.d., Member of Board of Directors, Wilkes-Barre General Hospital; Board of Health, Wilkes-Barre; Board of Directors, White Haven Sanitarium Association and Penna. Tuberculosis Society. 264 S. Franklin St., Wilkes-Barre, Pa.
1936. Richards, Alfred Newton, ph.d., sc.d., m.d. (hon.), l.l.d., Emeritus Professor of Pharmacology, School of Medicine and Associate Trustee, University of Pa.
1942. Russell, Frederick Fuller, m.d., Brig. Gen. Med. Corps, U.S.A. (Ret.). 4938 Brownsboro Road, Louisville, Kentucky.
1947. Stone, Robert Spencer, Univ. of California Medical School, San Francisco, Calif.

Foreign

1937. Dale, Sir Henry Hallett, c.b.e., f.r.s., m.a., m.d., f.r.c.p., Director, National Institute for Medical Research, The Wellcome Trust, 28 Portman Sq., London, W. C. England.
1922. McCarrison, Sir Robert, k.t., c.i.e., m.d., d.sc., ll.d., f.r.c.p., Major-General, Indian Medical Service (retired). 18 Linton Rd., Oxford, England.

Necrological List

Resident Fellows	*Date of Election*	*Date of Death*
G. Mason Astley	October 6, 1920	January 15, 1954
Sydney G. Biddle	May 7, 1934	October 28, 1954

Ralph Butler	May 2, 1906	March 3, 1954
George H. Cross	October 6, 1920	November 23, 1954
John Eiman	January 6, 1930	December 3, 1954
Jacques L. Guequierre	May 9, 1932	January 15, 1954
Charles R. Heed	January 4, 1911	May 23, 1954
John E. Hume	January 3, 1923	September 6, 1954
Rutherford L. John	January 9, 1928	January 24, 1954
Balduin H. E. Lucké	October 5, 1921	April 26, 1954
Edward F. McLaughlin	September 25, 1940	May 31, 1954
Norman Rothschild	January 6, 1936	February 20, 1954
Hunter W. Scarlett	January 7, 1920	December 23, 1954
Francis W. Sinkler	February 6, 1907	January 2, 1954
George B. Wood	February 7, 1900	November 2, 1954

Non-Resident Fellows

Norman B. Gwyn	June 4, 1902	February 1, 1952
John H. Jopson	February 1, 1899	December 4, 1954

Honorary Fellow

John Alexander	January 4, 1949	July 16, 1954

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